

# Trial of labour after caesarean



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# **Trial of labour after caesarean**

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To my lovely and great family



# ABSTRACT

## Background

Induction of labour and caesarean delivery are common interventions in obstetric care and over the last decades both have been steadily increasing in frequency worldwide. The two interventions are concatenated, since many of the indications for either intervention often are the same, and approximately 20-40% of all inductions in first time mothers ends with a caesarean delivery. Women with a caesarean delivery are in their next pregnancy and delivery at risk for both maternal and neonatal adverse outcomes. The aim of this thesis was to study the woman's chances of a vaginal birth after a first caesarean delivery, and her risk of having a repeat caesarean, in the light of the previous reason for the first caesarean. And also study the risk of a negative birth experience depending on delivery mode after a trial of labour after caesarean. Predicting a woman's probabilities of a vaginal birth could facilitate the antenatal decisions. Having a previous vaginal birth is one of the strongest predictors for a vaginal birth after caesarean. Delivery mode in women with only a caesarean delivery is more unpredictable. Therefore we aimed to develop a prediction model to predict vaginal birth in women with only a previous caesarean delivery. A further aim was to study the differences in time-to-delivery, caesarean delivery rate, and other maternal and neonatal outcomes between different induction methods in nulliparous women with an unripe cervix.

## Material and methods

In these population-based studies we used two different data cohorts based on pregnant women's antenatal, delivery and postnatal electronic medical records. The Stockholm-Gotland Obstetric Cohort includes the whole population of women delivering in the region and includes approximately 25% of all births in Sweden. The study period was over 7 years, between 2008 and 2014 (Study I, II, IV). The Swedish Pregnancy Register is a new register that has been in use since 2013, today covering 98.5% of all deliveries in Sweden. In our cohort the women studied had two following deliveries between 2014 and 2017 (Study III). In all four studies all the pregnancies and deliveries were at or beyond term, with a singleton infant, in cephalic presentation and live born. The induced women in Study I were nulliparous and in studies II, III and IV the women had one previous caesarean delivery. By using different regression analyses (linear, logistic and Poisson) we calculated time-to-delivery, adverse outcomes, risk of repeat caesarean, mean birth experience and risk of negative birth experience in study I, II and III. In study IV we used both regression and machine learning methods (conditional inference tree and random forest, lasso binary regression) to develop prediction models for predicting vaginal birth after caesarean.



## Results

When labour was induced in first time mothers, compared to dinoprostone, an association of a 7 hour shorter mean time-to-delivery with balloon catheter was found, and 1.5 hour shorter mean time-to-delivery with misoprostol. The caesarean delivery rates were high, but the different induction methods showed no significant difference with regard to adverse outcomes. Of all women undergoing a trial of labour after caesarean, 69% had a vaginal delivery. Women with a first unplanned caesarean had increased risk of repeat caesarean compared to women with elective first caesarean (risk ratio 1.64, 95% confidence interval 1.43-1.89). With a previous labour dystocia the risk of repeat caesarean in the second labour was almost twofold. In women with a history of labour dystocia the risk for repeat caesarean decreased with increasing cervical dilation at first delivery. Mean birth experience was rated high for all women, but having an unplanned repeat caesarean was associated with an increased risk of negative birth experience. Machine learning and classical regression models had an area under the receiver-operating curve ranging between 0.61 to 0.69, with a high sensitivity and a low specificity in predicting vaginal birth in women with one previous birth, a caesarean delivery.

## Conclusions

To be induced with a balloon catheter is associated with a shorter time-to-delivery than prostaglandins. Induced women have high caesarean rates. Almost 70% of all eligible women deliver vaginally after a trial of labour after caesarean, even women with a history of labour dystocia have a good chance. Most women with a first caesarean score their next birth experience as positive, irrespective of the mode of delivery. However, having a repeat unplanned caesarean is associated with the risk of a negative birth experience. To predict vaginal birth after caesarean is difficult. All the models misclassified unplanned repeat CDs, the majority of individuals with an unplanned repeat CD in the second delivery, had a predicted probability of more than 60% chance of giving birth vaginally.

## Key words

Induction of labour, caesarean delivery, trial of labour after caesarean, vaginal birth after caesarean

## LIST OF SCIENTIFIC PAPERS

- I. **Time-to-delivery and delivery outcomes comparing three methods of labor induction in 7551 nulliparous women: A population-based cohort study**

Charlotte Lindblad Wollmann, Mia Ahlberg, Sissel Saltvedt and Olof Stephansson

*Journal of Perinatology (2017) 00, 1-7*

- II. **Risk of repeat cesarean delivery in women undergoing trial of labor: A population-based cohort study**

Charlotte Lindblad Wollmann, Mia Ahlberg, Sissel Saltvedt, Kari Johansson, Charlotte Elvander and Olof Stephansson

*AOGS 2018;00:1-6*

- III. **Risk of negative birth experience in women with a previous caesarean delivery: A population-based cohort study**

Charlotte Lindblad Wollmann, Can Liu, Sissel Saltvedt, Charlotte Elvander, Mia Ahlberg and Olof Stephansson

*Submitted for publication*

- IV. **Predicting vaginal birth after cesarean using machine learning models**

Charlotte Lindblad Wollmann, Kyle Hart, Can Liu, Aaron B. Caughey, Olof Stephansson and Jonatan M. Snowden

*Submitted for publication*

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## LIST OF ABBREVIATIONS

AUROC	Area under the receiver-operating characteristics curve
BMI	Body Mass Index
CD	Caesarean Delivery
CI	Confidence Interval
CTG	Cardiotocography
ERCD	Elective Repeat Caesarean Delivery
OR	Odds Ratio
RR	Risk Ratio
TOLAC	Trial Of Labour After Caesarean
µg	microgram
VAS	Visual Analogue Scale
VBAC	Vaginal Birth After Caesarean
WHO	World Health Organisation

# 1 INTRODUCTION

To give birth is a unique event in a woman's life. During pregnancy, I awaited giving birth with great anticipation, delight and sometimes even with fear. Afterwards lying in bed with a completely new person in my arms was an unbelievable feeling. I have given birth to this wonderful and beautiful little boy! Or have I really given birth? I had an unplanned caesarean delivery. Doubts about having given birth, a feeling of failure and a wish for revenge came to me stealthily. In next pregnancy I would show them!

During preparations for my next delivery I collected more information, went to evening events with different advice; Don't use epidural anaesthesia! Stand upright! Don't be passive! Full of revenge desire, I handled the first hours of strong contractions well. However, after many hours of not enough progress of labour, we came to the operation theatre with the promise of an attempt of vacuum extraction. Another caesarean! What a failure! But still a wonderful girl! I was happy but at the same time sad. After two caesareans there would be no more chance of vaginal birth for me.

What are my reflections today, after four caesareans and four wonderful children nineteen years after that first birth? I wish I had had a dedicated, engaged and present midwife at my first delivery, not a midwife overloaded with work, without enough time for me. I also wish that I had had an individual plan during the following pregnancy, giving me evidence-based explanations and realistic expectations about the next birth. I also wish I had been induced in the first pregnancy instead of letting me wait until 43 full pregnancy weeks. However, I am very happy and fortunate that at the end, I have four healthy children and have experienced no adverse outcomes, other than the actual caesareans. I am happy and very fortunate to live, give birth and work in a developed country like Sweden.

## 1.1 Interventions

Worldwide, when addressing maternal health one has implemented strategies to reduce maternal mortality by focusing on the causes of pregnancy related deaths, increased skilled birth attendance, giving birth in facilities, and an access to basic maternal health care. These strategies has been partly successful, although maternal mortality and morbidity has not decreased as rapidly as hoped. Still care is insufficient, this is in the literature referred to as "too little, too late". The increase of births in facilities in some parts of the world has, on the other hand, led to an overuse of interventions and an over-medicalisation of birth, "too much, too soon".<sup>1</sup>

The aim of health care professionals in obstetrics is a healthy mother and infant and to avoid unnecessary interventions as well as to achieve a low frequency of morbidity and mortality. However, the frequency of caesarean deliveries (CDs) has increased over the last decades without any corresponding decrease in mortality and morbidity.<sup>2</sup>

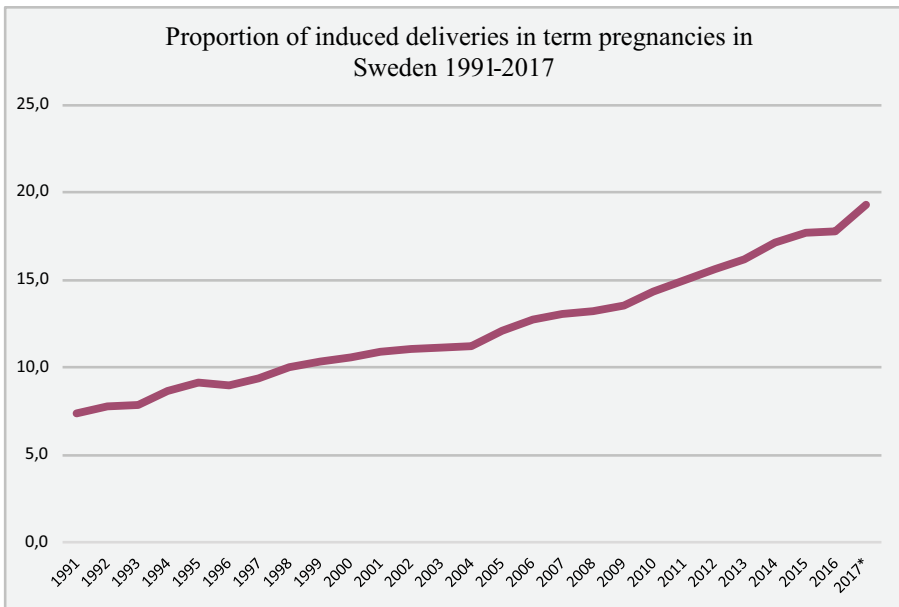
In low risk pregnancies and labour processes, emphasis has been put on women's and clinician's shared decisions for obstetric interventions that are both evidence-based and patient-centred. The base for performing an intervention is the knowledge of its risks and benefits for both the woman and her child. It is often discussed and believed that one intervention leads to a "cascade" of further obstetric interventions.<sup>3, 4</sup> This cascade of interventions may start as early as when the woman is presented to the delivery ward, and the earlier the intervention begins the greater the probability of progress to other interventions with the cascade down to caesarean delivery.<sup>4</sup> It is of great importance to better understand this cascade to be able to reduce the caesarean delivery rates.<sup>4</sup>

Both the induction of labour and the caesarean delivery are common interventions in obstetric care. They are necessary but often overused<sup>1</sup>, and over the last decades have been steadily increasing in frequency.<sup>2, 5, 6</sup> These two interventions go hand-in-hand, since many of the indications for either intervention often are the same or concatenated, approximately 20-40% of all inductions in first time mothers ends with a caesarean delivery.<sup>7-12</sup>

## 2 INDUCTION OF LABOUR

### 2.1 Background

Labour induction is a common obstetrical intervention that has increased to up to 20% of all deliveries in many developed countries. In Sweden, 18% of all singleton deliveries at term were induced in 2017 (Figure 2.1).



**Figure 2.1.** Induction of labour; singleton at or beyond term. The National Board of Health and Welfare, the Swedish Medical Birth Register 1973–2017. \*In 2017, 3000 births are missing from region Skåne.

The goal of the induction of labour is to achieve a vaginal delivery before the spontaneous onset of labour. Induction is generally looked upon as a therapeutic action when the risk of induction outweighs the risks of prolonging the pregnancy. The benefits of induction must be weighed against the potential maternal and fetal risks.<sup>13</sup> Induction of labour has often the same indications as a caesarean delivery (CD); obstetric indications (e.g. postterm pregnancy, prelabour rupture of the membranes, choriamnionitis, preeclampsia or diabetes) but can also be performed due to fetal indications (e.g. non-reassuring fetal monitoring, intrauterine growth restriction, oligo- or polyhydramnios). Over the last decades, induction on maternal request has become more common.<sup>6, 14</sup>



The main clinical concern, and a subject for discussion over the world, is whether induction of labour increases the risk of CD, mostly due to failed induction or fetal distress caused by uterine hyperstimulation and prolonged delivery. There are studies suggesting that the induction of labour increases the risk of CD.<sup>7, 8, 11, 15</sup> Later studies comparing induction of labour with expectant management, as well as randomised studies, have come to other conclusions, as described below.

### **Prelabour rupture of the membranes**

A Cochrane systematic review, comparing induction of labour and expectant management in women with prelabour rupture of the membranes at 37 weeks' gestation or more, concluded that induction (with methods such as oxytocin or prostaglandin) reduces the risk of maternal infections without increasing CDs or operative vaginal births, and fewer infants went to neonatal intensive care.<sup>16</sup> A study by Hannah et al. comparing women randomly assigned for induction of labour or expectant management for prelabour rupture of the membranes at term found that women viewed induction more positively than expectant management and there was no significant difference in CD rates (10.1% CD in the induction group compared to 9.7% in the expectant management group, odds ratio (OR) 0.9; 95% confidence interval (CI) 0.7-1.1) or neonatal infection between the groups.<sup>17</sup>

### **Gestational hypertension or mild preeclampsia**

In the "HYPITAT" study, 756 women with gestational hypertension or mild preeclampsia were randomised to either induction of labour or expectant management, 31% and 44% respectively developed a composite of poor maternal outcomes as maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, and placental abruption), progression to severe disease, or major post-partum haemorrhage, (relative risk (RR) 0.71, 95% CI 0.59-0.86,  $p < 0.0001$ ). In absolute numbers rates of CDs were higher in the expectant management group, although it was a non-significant difference (14% vs 19%, RR 0.75, 95% CI 0.55-1.04,  $p = 0.085$ ).<sup>18</sup>

### **Maternal request**

Induction of labour on maternal request/ without medical indication is debated and has shown contradictory results. A large retrospective study from Scotland, comparing induction on maternal request with women continuing pregnancy to either spontaneous labour, induction of labour or CD at a later gestation, concluded that elective induction at term can reduce perinatal mortality without increasing the risk of operative delivery.<sup>19</sup> However, in a study from New York State, with a similar design as the Scottish study, an association of an increased risk of CD after induction of labour on maternal request was found.<sup>8</sup> A meta-analysis by Mishanina et al. published 2014, concluded that their "analysis provides a robust answer to

the disputed question of risk of CD associated with induction of labour'. Women whose labour was induced were less likely than those managed expectantly to have a CD.<sup>20</sup> Recently, a randomised study by Grobman et al. randomised low-risk nulliparous women to either labour induction in gestational week 39+0 to 39+4 or expectant management with delivery induced, if needed, at earliest 40+5 weeks and no later than 42+2 weeks. The conclusion was that induction in the 39<sup>th</sup> week did not result in a lower frequency of adverse composite neonatal outcome, although it did result in a lower frequency of CDs (18.6% vs. 22.2%; RR 0.84; 95% CI 0.76-0.93).<sup>21</sup>

### **Postterm pregnancy**

There are randomised studies showing that there is an association of increased risk of maternal and fetal adverse outcomes at late term pregnancy in comparison with term pregnancy. A Cochrane review including 30 randomised controlled trials that studied women at or beyond term where the women either had a labour induction or were treated with a policy of expectant management.<sup>22</sup> They found that a policy of labour induction was associated with fewer perinatal deaths (RR 0.33, 95% CI 0.14-0.78) and fewer CDs (RR 0.92, 95% CI 0.85-0.99) and a marginal increase in operative vaginal deliveries (RR 1.07, 95% CI 0.99-1.16). Most studies had a policy of induction at 41 weeks in the intervention arm. The conclusion was that the absolute risk of perinatal death was small and that the optimal timing of induction of labour warrants further investigation.<sup>22</sup>

In a multicentre randomised study from the Netherlands, they compared induction in gestational week 41 with expectant management and induction in gestational week 42.<sup>23</sup> A significant difference of 1.4% was found for the risk of adverse perinatal outcomes when management was expectant, but the chances of a good perinatal outcome were high with both managements. There were no significant difference in composite adverse maternal outcomes or in CD rate.<sup>23</sup>

A Swedish multicentre register based randomised controlled trial, SWEPIS, compares induction of labour at 41 completed gestational weeks with expectant management and induction at 42 completed gestational weeks. Their primary outcome is a composite of stillbirth, neonatal mortality and severe neonatal morbidity.<sup>24</sup> This study is still under analysis and no final results has yet been presented at the time of writing this thesis.

### **Fetal macrosomia**

In a Cochrane analysis from 2016 reviewing whether to induce labour in women with suspected fetal macrosomia it was concluded that the induction of labour did not significantly increase CD rates, but that the incidence of shoulder dystocia and infant fracture was significantly lower in the group where labour was induced.

This review was based on four trials with 1190 women, of which the largest trial included 822 women who were randomised to induction between 37+0 and 38+6 gestational weeks or expectant management, with a mean birthweight of 3831 g in the induction group. The conclusion from reviewers was that more randomised studies are needed.<sup>25, 26</sup> In another review of same four trials, by Magro-Malosso et al., they concluded that it may be reasonable to induce women for suspected fetal macrosomia, since the CD rates were the same in the induction group as in the expectant management group, even though there was no difference in the rates of shoulder dystocia, intracranial haemorrhage or brachial plexus palsy.<sup>27</sup> There were two limitations with the largest randomised trial included in this review by Magro-Malosso et al.; the women from the largest trial represented almost 70% of all patients. Moreover, there were also diabetic women included in the study, introducing a bias of diabetes with its concomitant risk for shoulder dystocia. In the meta-analysis a significant reduction of fractures was found.<sup>27</sup> In a comment, published in BJOG 2016, Norwitz states that these fractures must refer to clavicular fractures and that the diagnosis of them is often inaccurate, and if correctly diagnosed, the prognosis is benign with no sequelae.<sup>28</sup> Recently, in a nationwide population-based Swedish cohort study by Moldeus et al. they compared non-diabetic women with large for gestational age infants (>90<sup>th</sup> centile) induced at 38 completed gestational weeks with expectant management. Women in the expectant management group delivered after 39, 40, 41 or 42 completed gestational weeks, either by labour induction or spontaneous onset of labour. This study had the opposite results, emphasising the need for more studies. Women induced at week 38 had a significantly increased risk of CD (aOR 1.44, 95% CI 1.20-1.72) compared with expectant management. There was no difference in 5-minute Apgar<7 or infant birth injury. Similar results was seen when comparing induction of labour at week 39, 40, 41 compared to expectant management.<sup>29</sup>

Other complications with induction of labour in general, include prolonged labour with complications such as increased postpartum haemorrhage, chorionamnionitis and admission to the neonatal intensive care unit.<sup>30</sup>

In summary, it is convincingly shown that induction of labour due to prelabour rupture of the membranes, hypertensive disease during pregnancy or on maternal request (no medical indication) is not associated with an increased risk of CD when compared to women with an expectant management. But whether to induce labour due to suspect fetal macrosomia or not, or when to induce a postterm woman, is not yet sufficiently studied.<sup>16-21, 25</sup>

## **2.2 Bishop Score**

Cervical ripening is an important part of parturition, and includes remodelling through collagen breakdown, rearrangement and change of glucosaminoglycans,

increased production of cytokines and infiltration of the white blood cells.<sup>31</sup> When inducing labour, the degree of ripening of cervix will guide the choice of method. To be as objective as possible in assessing the cervix, the modified Bishop Score is most commonly used where the cervical position, consistency, effacement and dilation are assessed and the engagement in pelvis of the presenting part is also assessed, giving points between 0 and 10 (Table 2.1).<sup>32, 33</sup> An unfavourable cervix has been defined as a Bishop Score of 6 or less in most studies.<sup>13</sup>

**Table 2.1.** Modified Bishop Score

Points	0	1	2
Engagement of the presenting part	above/at pelvis-entrance	above spinae	at/below spinae
Cervical position	posterior	mid	anterior
Cervical consistency	firm	intermediate	soft
Cervical effacement	none	≤ 50 %	> 50 %
Cervical dilation	≤ 0.5 cm	> 0.5 - ≤ 1.5 cm	> 1.5 cm

## 2.3 Methods for induction of labour

### Prostaglandin and intracervical balloon catheter

The most common medical cervical ripening methods are the synthetic prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). An advantage of using prostaglandins for induction of labour is their efficiency when the cervix is unripe. The efficiency is a result of the pharmacological synergism between cervix ripening and stimulation of the myometrium. A disadvantage of prostaglandins is the risk of uterine hyperstimulation, which may be a risk factor for the development of fetal hypoxia.<sup>34</sup>

Misoprostol (a synthetic PGE<sub>1</sub>-analogue) can be administered either vaginally, orally or sublingually. The studied doses of misoprostol are mainly 25 or 50 micrograms (µg) for the induction of labour. There are many published studies and clinical experiences that support the safety and efficacy of misoprostol when it is used appropriately. The adverse maternal and fetal outcomes that has been reported in different studies results from using doses above 25 µg. An overdose may lead to hyperstimulation of the uterus and the accompanying fetal distress.<sup>34</sup> Cervical ripening with PGE<sub>2</sub> is, according to RCOG guidelines from 2008, the golden standard.<sup>14</sup> There are two frequently used and available PGE<sub>2</sub> forms in Sweden; dinoprostone vaginal gel (2 mg or 1 mg) or dinoprostone vaginally applied pessary (10 mg).

In a Cochrane review comparing oral misoprostol versus placebo/vaginal misoprostol/dinoprostone or oxytocin, the conclusion was clear: “Oral misoprostol as an induction agent is effective at achieving vaginal birth. It is more effective than placebo, as effective as vaginal misoprostol and results in fewer caesarean deliveries compared to vaginal dinoprostone or oxytocin”. And they further concluded “If using oral misoprostol, the evidence suggests that the dose should be 20 to 25 µg in solution. Given that safety is the primary concern, the evidence supports the use of oral regimens over vaginal regimens” (Table 2.2).<sup>13, 14, 34</sup>

Mechanical methods used for inducing labour were the first methods developed for ripening the cervix. Laminaria tents, made of sterile sea-weed or synthetic hydrophilic materials, introduced into the cervical canal, which enlarge the canal due to their hydrophilic properties.<sup>35</sup> A common method is a balloon catheter introduced through the cervical canal, eventually into the extra-amniotic space, inflated with fluid and then applied with traction. The ripening is mediated by the mechanical dilation of the cervical canal and through an indirect increasing of prostaglandin or oxytocin secretion. The balloon catheter may also stimulate the neuroendocrine reflexes and thereby the onset of contractions.<sup>13</sup>

In a Cochrane review published in 2012, the conclusion was that mechanical methods had similar CD rates as prostaglandins, but a lower risk of hyperstimulation of the uterus.<sup>36</sup> This was also confirmed in two later randomised studies by Penell et al.<sup>10</sup> and the PROBAAT-I study by Jozwiak et al.<sup>37</sup> Further, in the Cochrane analysis, the proportion of multiparous women induced mechanically who had not delivered vaginally within 24 h was higher compared with inducing with vaginal dinoprostone. Compared with oxytocin, the mechanical methods had a reduced risk of CD.<sup>36</sup> The PROBAAT-I study reported that dinoprostone had a shorter median time from start of induction to delivery, but this difference was only seen in the first 36 h.<sup>37</sup>

In the PROBAAT-II study by Eikelder et al. induction with misoprostol compared with balloon catheter was shown to result in a larger proportion of women delivered within the first 24 h, but after 36 h a larger proportion of women had delivered in the balloon catheter group.<sup>38</sup> A study by Prager et al.<sup>9</sup> comparing dinoprostone, vaginal misoprostol and balloon catheter showed on the contrary that balloon catheter induction led to a time-to-delivery that was about four hours shorter than the prostaglandin methods.<sup>9, 38</sup> (Summary in Table 2.2.)

**Table 2.2.** Summary of review or randomised studies comparing different induction methods

Type of study	Author, Journal, Year	Population	Comparing	Results
Syst. Review	Alfiervic et al. Cochrane 2014 <sup>34</sup>	76 RCTs (14412 women)	<b>Oral misoprostol</b> versus <b>placebo/ vaginal dinoprostone/ vaginal misoprostol/ oxytocin</b>	<b>Oral misoprostol</b> is effective at achieving vaginal birth. It is more effective than placebo, as effective as vaginal misoprostol and results in <b>fewer CDs than vaginal dinoprostone or oxytocin.</b>
Syst. Review	Jozwiak et al. Cochrane 2012 <sup>36</sup>	71 RCTs (9722 women)	<b>Mechanical methods</b> versus <b>no treatment/ vaginal dinoprostone/ misoprostol/oxytocin</b>	<b>Mechanical methods</b> result in <b>similar CD rates but less hyperstimulation compared to prostaglandins.</b> Proportion of multiparous women not delivered vaginally within 24 h was higher compared with vaginal dinoprostone. <b>Compared to oxytocin, reduced risk of CD.</b>
RCT	Prager et al. BJOG 2008 <sup>9</sup>	592 women	<b>Balloon catheter</b> versus <b>vaginal misoprostol/ dinoprostone</b>	<b>Balloon catheter: Shortest time-to-delivery (- 4 h).</b> No differences in neonatal and maternal outcome. Prostaglandins had the same effect.
RCT	Pennell et al. BJOG 2009 <sup>10</sup>	330 nulliparas	<b>Double balloon catheter</b> versus <b>single balloon catheter/ dinoprostone gel</b>	<b>No differences in CD rates.</b> Time-to-delivery longer in double balloon group. PGE2 group: More uterine hyperstimulation and worse cord blood samples. Less pain in single balloon group.
RCT	PROBAAT-I Jozwiak et al. Lancet 2011 <sup>37</sup>	824 women	<b>Dinoprostone</b> versus <b>balloon catheter</b>	<b>Balloon catheter:</b> Fewer CDs due to suspected fetal distress. Less treatment with intrapartum antibiotics. Longer time-to-delivery, more oxytocin. Fewer to neonatal ward. <b>No difference in CD and operative vaginal delivery rates.</b>
RCT	PROBAAT-II Eikelder et al. Lancet 2016 <sup>38</sup>	1859 women	<b>Oral misoprostol (50 µg/4h)</b> versus <b>balloon catheter</b>	<b>No difference in CD rate. More vaginal operative deliveries in misoprostol group (RR 1.45).</b> No differences in maternal and neonatal outcome. More women had delivered in misoprostol group within 24 h, but after 48 h more had delivered in balloon group.

Two-step induction or sequential induction, refers to a mechanical method used after prostaglandin or vice versa, initiated if the first method did not have a sufficient effect on cervix ripening. This is often used, but not well studied and therefore making it difficult to reach conclusions.

Recently, in a randomised controlled trial comparing a mechanical method (double-balloon) used simultaneous with either misoprostol 50 µg orally taken or placebo, resulted in no difference in CD rates, but time-to-delivery was significantly shorter when using both methods ( $14.6 \pm 6.9$  versus  $20.8 \pm 13.8$  hours,  $p < 0.0001$ ) and use of oxytocin was significantly less frequent ( $86.9$  versus  $98\%$ ,  $p = 0.01$ ).<sup>39</sup>

### **Other methods**

Amniotomy or artificial rupture of the membranes may be used as an induction method in women who have a more favourable cervical ripening (Bishop Score  $\geq 6$ ). But it is also used as the next step of induction in women after ripening of the cervix. Then amniotomy is often followed by the use of oxytocin. The evidence for amniotomy alone as an induction method is insufficient. However, in a study of amniotomy combined with early oxytocin infusion, time-to-delivery was shorter than with amniotomy alone.<sup>40</sup> This was later confirmed in a Cochrane review, where fewer women with amniotomy and oxytocin intravenous had not delivered vaginally after 24 hours than those with amniotomy alone (RR 0.03 95% CI 0.0001-0.49).<sup>41</sup>

Oxytocin stimulates labour in a way similar to spontaneous labour, but patients can vary in their response to the drug. This is partly dependent on gestational age, with an increase in response from 20 to 30 gestational weeks. After 30 gestational weeks there is a plateau in the response and at term, sensitivity increases again.<sup>13, 42</sup> Cervical dilation, parity, gestational age and body mass index are factors influencing the response to oxytocin. With oxytocin-infusion, the uterus normally responds within 3 to 5 minutes and steady-state levels are reached within 40 minutes.<sup>13, 42</sup>

Membrane sweeping is a simple method that even can be performed outside the hospital. The health provider introduces a finger into the endocervical os and the inferior pole of the membranes are detached from the lower uterine segment by sweeping the examining finger in a circular movement. This can initiate prostaglandin production and the onset of labour. It may be accompanied by discomfort during the vaginal examination, and bleeding and irregular contractions later on. In a Cochrane review it was concluded that membrane sweeping increases the likelihood of spontaneous onset of labour and reduces the frequency of pregnancies beyond 41 gestational weeks. There was no difference in CD rates in comparison with no treatment. The number needed to treat to avoid one induction of labour was 8.<sup>43</sup>

Nipple stimulation is a nonmedical, natural method for inducing labour, and in a systematic review, compared with no intervention there was a significant decrease in the number of women not being in labour within 72 h. However, this was seen only in women with a riper cervix. It was also associated with lower postpartum hemorrhage.<sup>13</sup>

Sexual intercourse as an induction method is very poorly studied. Only one study with 28 women was included in a Cochrane review from 2001. Human semen contains prostaglandin, but the role of sexual intercourse is not clear. It could be a result of the stimulation of the lower uterine segment or the endogenous oxytocin that is released during an orgasm. The conclusion was, however, that this is an important issue to the woman and her partner and that further randomised studies are needed.<sup>44</sup>

Acupuncture or acupressure is used during labour for stimulating contractions and as a pain relief. The hypothesis is that the neurogenic stimulation increases the contractions of the uterus and acts as an induction method. A Cochrane review from 2017 showed no clear benefit of acupuncture or acupressure.<sup>45</sup>

Mifepristone (an anti-progesterone) is not very well studied as an induction method, although in a Cochrane analysis from 2009 it was shown that it is better than placebo in reducing the CDs performed due to failed induction of labour, but the effects on the infant have not been studied in any depth. More studies are needed before using mifepristone as an induction agent in the clinics.<sup>46</sup>

Although there are many studies on labour induction methods, it is still not convincingly shown which method is safest and most effective in nulliparous women with an unripe cervix with respect to the length of labour, mode-of-delivery, maternal and neonatal outcomes.



## 3 THE FIRST CAESAREAN

### 3.1 History of caesarean delivery

Julius Caesar is said to have been born (100 B.C.) through a caesarean procedure, although, this is unlikely since his mother was said to live as he invaded Britain. According to a Roman law “Lex Regia”, already around 700 B.C., women dying or already dead through childbirth should be cut open in an attempt to save the life of the child, and the law forbade the burial of a pregnant woman before the child had been extracted from the womb. When Ancient Rome became the Roman Empire they changed the name of the law from “Lex Regia” to “Lex Cesarea”.<sup>47</sup> Other explanations for the name Caesarean could be the Latin word “caedere” which means to cut.

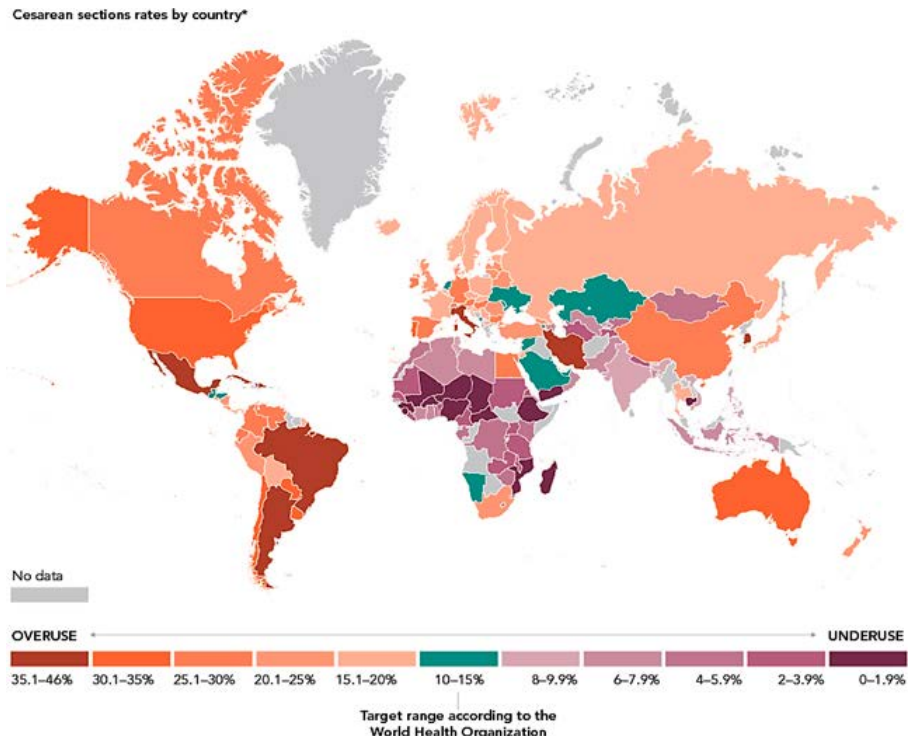
One of the first written reports, from year 1500, is of a woman and child surviving a caesarean procedure, performed by Jacob Nufer, a Swiss sow-gelder (a person who sterilise female pigs), on his own wife after several days of labour. However, this is not fully accepted as true since this was first reported in 1581. In 1581 Francois Rousset published a work describing the caesarean method and also reasons for performing the caesarean section; large fetus, malformed fetus, dead fetus, twins, malpresentation.<sup>47</sup>

The first caesarean delivery in Sweden was performed 1758 by Schützer, a surgeon who was the queen’s chief physician. However in the 13 caesareans performed between 1758 and 1875, all women died. The operations were performed on women who had been in labour for several days. Later in 1875, there are descriptions of 24 women undergoing caesarean deliveries under better surgical conditions with a survival rate of 75%. An important development in increasing maternal safety and reducing death was the introduction of suturing the uterus, first introduced by Lebas in 1769, later Max Sanger insisted on this in 1882.<sup>47, 48</sup>

In the late 19<sup>th</sup> century and beginning of the 20<sup>th</sup> century in U.S. and Europe, labour was moved into hospitals for women living in the cities. Obstetricians argued for earlier caesarean deliveries when labour was protracted, and more women had the chance to have a caesarean when needed as it became safer. In addition the availability of safe anaesthesia and antibiotics decreased the maternal and infant perinatal mortality rates.<sup>48</sup> In Sweden between 1951 and 1955 the maternal mortality rate decreased to 0.5% when blood transfusions, parenteral infusions, uterotonic drugs, thrombosis prophylactics and antibiotics became a part of routine obstetrical care.<sup>49, 50</sup>

### 3.2 Rates of caesarean deliveries

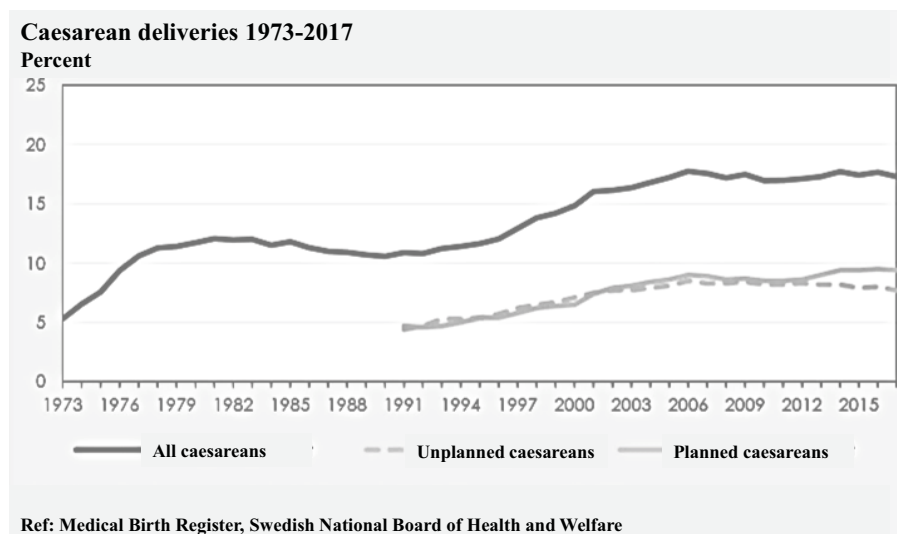
In 1985 the World Health Organisation (WHO) recommended a caesarean delivery rate of 10-15%. In a later document from 2015, WHO stated that CD rates above 10% of a population level are not associated with a reduction in maternal and newborn mortality rates. As CD rates increased above 10% and even up to 30%, no further positive effect on maternal and neonatal mortality was seen (Figure 3.1). Effects on stillbirth and morbidity rates could not be assessed due to lack of data at the population level. But WHO also concluded that CD should be provided to women who needs this rather than to strive for specific rates.<sup>2</sup>



*Figure 3.1. WHO report Gibbons et al. 2010*

From 1990 to 2006, the rate of CDs overall in Sweden rose from 11% to 18%,<sup>49</sup> and has been stable since then with today's rate of 19% (Figure 3.2).<sup>6, 12</sup> The rise in CD rates has partly been explained by changes in obstetrical care, for example, today 94% of women with breech presentation deliver with CD. High maternal age, high body mass index (BMI) and nulliparity are considered risk factors for CD, and as maternal age and BMI have both increased during the last decades, this might have contributed to the high CD rates. In a report by the Swedish

Medical Birth Register from 2005, it is shown that CDs on maternal request has increased, however these deliveries only constitute 4.6% of all CDs (9.7% of all elective CDs).<sup>5, 6, 49</sup>



**Figure 3.2.** Rate of caesarean deliveries 1973-2017, The Swedish Medical Birth Register  
Dark grey line: All CDs, Light grey line: Planned CDs, Dotted line: Unplanned CDs

In the U.S the CD rate increased from 5% to more than 31% between 1970 and 2007, as a result of several changes in obstetrical practice; the introduction of electronic fetal monitoring, decreased amount of breech vaginal deliveries and forceps deliveries. It was also an opinion flourishing, that “once a caesarean always a caesarean”.<sup>51</sup> However, changing the attitude of once a caesarean always a repeat caesarean, increased rates of vaginal births after caesarean, and this led to decreased CD rates (20%) in 1996. Later when more women underwent trial of labour after caesarean (TOLAC), the frequencies of uterine rupture and other complications increased, resulting in today’s caesarean rates of 32%. In 2002 only 12.7% of women in U.S. with one previous CD had a vaginal delivery in subsequent pregnancy.<sup>52-54</sup>

There has been a lack of consistency when comparing CD rates regarding women’s obstetrical history, and there was no international classification system that would facilitate comparison between countries and regions. After being thoroughly reviewed by experts, a classification system based on the women’s obstetric characteristics, by Dr Michael Robson in 2001, was proposed by WHO to be used from 2014 as an international system to classify pregnant women admitted for

delivery.<sup>2,55,56</sup> This classification system stratifies women exclusively into ten different groups based on parity, onset of labour, gestational age, fetal presentation and number of fetuses and thereby facilitates comparison of CD rates with fewer confounding factors (Figure 3.3).<sup>55</sup>



**Figure 3.3. Robson Classification, WHO**

### 3.3 Indications of caesarean delivery

Another way to compare CD rates, and to better understand the underlying reasons for performing a CD is to study the indications for the CDs. The different reasons could either be due to elective, planned indications or unplanned, emergency indications.<sup>5, 49</sup>

#### 3.3.1 Unplanned indications

##### Labour dystocia

Labour dystocia, or arrest of labour, is the main cause of primary unplanned CD and also contributes to a great number of repeat CDs.<sup>5, 57</sup> Labour dystocia can be diagnosed in the active phase of first stage or in the second stage of labour.<sup>58</sup> Dystocia is reported to have an increasing incidence and this could be due to several factors: increasing maternal age and overweight; fetal macrosomia; but also due to change in obstetrical practice over time with more use of oxytocin and epidural analgesia; fewer instrumental vaginal deliveries; and of great importance, there is a lack of consensus in definition of the normal labour progress.<sup>58, 59</sup> About 12% of women with previous dystocia have a recurrence, and in women with a previous CD due to dystocia the recurrence rate is 34%.<sup>60</sup> A prolonged delivery is associated with risks for both the mother (haemorrhage, chorioamnionitis, endometritis and lacerations) and infant (birth asphyxia, meconium aspiration and shoulder dystocia).<sup>54, 58, 61</sup> However, dystocia is a complex condition and complex to study due to many associated diagnostic codes, and there is also no consensus on a precise definition when the active phase of the first stage of labour begins and how a normal labour progress is defined. In 2014, the American College of Obstetrics and Gynaecology defined the start of the active phase as when cervical dilation is 6 cm.<sup>62, 63</sup> However, in the NICE guidelines from 2014, the Royal College in the United Kingdom defined the start of labour as when the woman has regular, painful contractions and a progressive cervical dilation from 4 cm.<sup>64, 65</sup> In 2001, Sweden defined active labour as when the woman fulfilled two of three criteria; cervical dilation of 3-4 cm, three or more regular contractions every ten minutes, rupture of the amniotic membranes.<sup>66</sup>

The second stage of labour begins when the cervix is fully dilated and ends with the delivery of the infant. Parity, use of epidural analgesia, delayed pushing, maternal BMI, birth weight, and occiput posterior position of infant all have the possibility to affect the length of the second stage. To define an appropriate duration of the second stage is complicated, the short- and long-term maternal and neonatal outcomes must be considered. There are studies of nulliparous women concluding that a longer duration of active pushing, >3-4 hours, is not associated with adverse neonatal outcomes.<sup>67, 68</sup> However, in multiparous women, pushing for >3 hours is associated with an increased risk of neonatal morbidity (5-minute Apgar score

of <7, admission to the neonatal intensive care unit, and a composite of neonatal morbidity).<sup>69</sup> A longer second stage of delivery is associated with adverse maternal outcomes; higher rates of third- or fourth degree perineal lacerations, postpartum haemorrhage and infections.<sup>70</sup> Thereto the probability of reaching a vaginal delivery is decreasing with every hour of the second stage.<sup>70</sup> Still there is no clear cut off how long the duration of second stage may be.<sup>64</sup> Recently a consortium for preventing the primary CD in the U.S. and WHO, both recommending, when maternal and neonatal conditions permit, at least 2 hours of second stage in multiparous women and 3 hours in nulliparous women, before interrupting for operative delivery.<sup>64, 71</sup> In 2018, WHO published definitions of the different stages in labour in an attempt to harmonise these definitions and decrease CD rates due to dystocia.<sup>71</sup>

### **Failed induction of labour**

Failed induction of labour, also a common indication for CD where, despite many hours of induction with prostaglandins and/ or mechanical methods, or even many hours of an oxytocin infusion, the woman does not establish, or proceed, in the active phase of labour. There is a lack of consistency in guidelines; when to terminate an induction and proceed with a CD and most likely a variation in practice. Recommendations today, suggest allowing longer durations of the latent phase ( $\geq 24$  hours) and longer time of administrations with oxytocin (at least 12-18 hours) before stating a failed induction.<sup>64</sup>

### **Fetal compromise**

At the beginning of the 1900s, fetal monitoring during labour was performed through auscultation, for example with Pinard's horn. During the 1950s the technique of electronic fetal surveillance was developed. In the 1970s cardiotocography (CTG) was introduced in Sweden and became widely used in the latter part of the twentieth century to decrease the perinatal mortality.<sup>49</sup> A Cochrane meta-analysis of thirteen existing randomised trials stated that compared to intermittent auscultation, the use of CTG during labour was associated with halving the number of neonatal seizures and led to a significant increase in caesarean deliveries, but resulted in no differences in the rate of cerebral palsy or overall perinatal mortality. On the other hand, a meta-analysis from 1995, which excluded deaths not attributed to fetal hypoxia, reported a significant reduction in perinatal mortality.<sup>72, 73</sup> CTG is used as a standard fetal surveillance in most of the labour wards in developed countries today. One of the most common indications for unplanned CD is fetal compromise, including non-reassured fetal well-being, placental abruption, uterine rupture and umbilical cord prolapse.<sup>5, 57</sup> In an analysis of indications for CD over time, in Sweden between 1995 and 2006, fetal indication accounted for 12% of the increase of CDs. 31.7% of women with a single infant, in cephalic presentation that was delivered by a caesarean at or beyond 37 gestational weeks, had a CD due to fetal indication. Almost 1/3 of all CDs with the indication labour dystocia also had an indication for non-reassured fetal well-being.<sup>5, 49</sup>

### **3.3.2 Elective indications**

#### **Breech presentation**

Since the 1970s the number of vaginal breech deliveries has decreased in developed countries. After a randomised, multicentre trial by Hannah et al. published in 2000 with the conclusion that perinatal mortality, neonatal mortality, or serious neonatal morbidity was significantly lower for the elective caesarean section group than for the planned vaginal birth group<sup>74</sup>, the number of vaginal breech deliveries dropped further. These results have recently been confirmed in a meta-analysis, where they found that the relative risk for adverse outcomes in the neonate was increased as in the study by Hannah et al., but the absolute risks were comparable with the absolute risks for giving birth vaginally to an infant in cephalic presentation. This resulted in the recommendation to make an individualised decision on the route of delivery in women bearing an infant in a term breech presentation.<sup>64, 75</sup> In Sweden 94% of infants in breech presentation are born by CD.<sup>5, 49, 76</sup>

#### **Maternal request**

Caesarean delivery on maternal request has become more prevalent lately. In a study from the Swedish Medical Birth Register, for all births in Sweden, between 1996 and 2006, increased maternal age and increased BMI was the underlying cause of one third of the increased CD rates over the period.<sup>5</sup> CD on maternal request contributed to 8.5% of the increased CD rates. However, the maternal request CD rate over the period studied was only 4.6% of all CDs.<sup>5, 49</sup> There can be many underlying reasons for elective CD on maternal request, e.g. primary or secondary fear of delivery, sexual abuse, loss of trust for health care providers, anxiety or depression.<sup>77-79</sup> In a Swedish study comparing indications for CD at Karolinska University hospital in Stockholm, 10.5% and 38.5% of elective CD indications were a result of maternal request in 1992 and 2005 respectively. Among these women 23% were nulliparous, 23% had had a previous vaginal delivery and 54% had undergone a previous CD.<sup>80</sup>

#### **Placenta praevia**

Abnormal forms of placentation such as placenta praevia (placenta is lying over the endocervical os of the cervix), are managed with a CD. The incidence is about 1 in 200 term pregnancies but varies throughout the world.<sup>81</sup> The incidence is thought to have increased in relation with the increasing CD rates. In Sweden, placenta praevia appears in 0.3% of all deliveries.<sup>82</sup>

#### **Multiple infants**

Both with term di- and monochorionic twins, when the first twin is lying in cephalic presentation, vaginal delivery is internationally considered as the best option.<sup>83</sup> But when the first infant is not in cephalic presentation or the pregnancy is mono-

amniotic or very preterm (gestational age below 32 weeks) CD is recommended. CD is also generally recommended in triple (or more infants) pregnancy due to problems with monitoring with conventional CTG.<sup>49, 84, 85</sup>

### **Intrauterine growth restriction and preterm births**

Intrauterine growth restriction may be an indication of CD, especially when severe and/or fetal blood flow is pronouncedly affected as this predicts a great risk of intrapartal asphyxia.<sup>86</sup> In cases where there is a risk of preterm birth, it has not been shown that CD brings any benefits if the only indication of CD is prematurity. However in Sweden there is a consensus that when the infant is in breech position, placental insufficiency is present or there are other fetal indications, CD is usually to be preferred.<sup>87, 88</sup>

### **Other fetal or maternal factors**

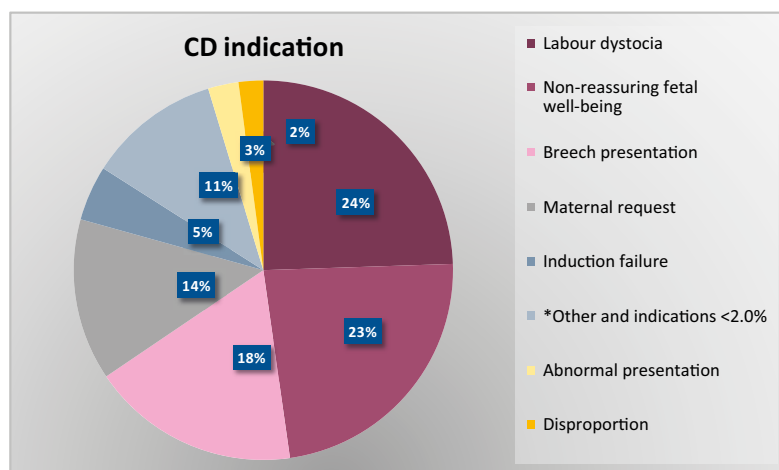
Infants  $\geq 4500$  g are considered to be macrosomic and based on consensus and expert opinion, elective CD may be considered for suspected fetal macrosomia in cases of an estimated fetal weight  $>5000$  g in pregnant woman without diabetes and  $>4500$  g in women with diabetes.<sup>64</sup> CD should also be considered when a prolonged second stage of labour or an arrest of descent occurs in patients with an estimated fetal weight  $>4500$  g. The clinical dilemma is that the diagnosis of macrosomia is imprecise and the prediction of shoulder dystocia is poor.<sup>64</sup> Fetal malformations or fetal thrombocytopenia, as well as different infectious diseases in the mother (e.g. HIV, Hepatitis B and Herpes Simplex) are rare conditions and *may* be indications of CD.<sup>49, 64, 83, 89</sup>

Other possible indications for an elective first CD are tumours in the delivery channel that form obstacles for vaginal delivery, permanent cervical cerclage after trachelectomy, vasa previa or previous vaginal or incontinence surgery.



**Table 3.1.** Summary CD rates by indication, and vaginal delivery rates in nulliparous women at or beyond term. The Stockholm-Gotland Obstetric database, 2008-2014

Nulliparous women, n = 76468			
Indication of CD	n (% of all CDs / % of all deliveries)		
Labour dystocia	3899 (24.5/5.10)	Macrosomia	149 (0.9/0.19)
Non-reassuring fetal well-being	3714 (23.3/4.86)	Placenta praevia	144 (0.9/0.19)
Breech presentation	2830 (17.8/3.70)	Intrauterine growth restriction	141 (0.9/0.18)
Maternal request	2193 (13.8/2.87)	Placental abruption	108 (0.7/0.14)
Induction failure	751 (4.7/0.98)	Obstetric history	96 (0.6/0.13)
Other	538 (3.4/0.70)	Pelvic disproportion	94 (0.6/0.12)
Abnormal presentation	410 (2.6/0.53)	Previous uterine operation	93 (0.6/0.12)
Disproportion	339 (2.1/0.44)	Prolapse of umbilical cord	40 (0.3/0.05)
Preeclampsia	196 (1.2/0.26)	Diabetes	15 (0.1/0.02)
Missing indication	176 (1.1/0.23)		
<b>Total CD, n (%)</b>	<b>15926 (20.8)</b>		
<b>Instrumental vaginal deliveries, n (%)</b>	<b>11175 (14.6)</b>		
<b>Non-instrumental vaginal deliveries, n (%)</b>	<b>49367 (64.6)</b>		



**Figure 3.4.** Summary CD rates of all CDs by indication in nulliparous women at or beyond term. The Stockholm-Gotland Obstetric database, 2008-2014

\* Including, from Table 3.1: Other, preeclampsia, missing indications, macrosomia, placenta praevia, intrauterine growth restriction, placental abruption, obstetric history, pelvic disproportion, previous uterine operation, prolapse of umbilical cord, and diabetes

### 3.4 Maternal risks with caesarean delivery

#### 3.4.1 Short term risks

Birth complications are not rare in vaginal births but are more frequent in CDs. These complications can be minor or severe and can occur immediately (short term) or have long-term consequences. Studies consistently show that CD is associated with small but measurable increased maternal and neonatal risks when compared with vaginal delivery. These risks include infection, blood transfusion, injury, death of mother or infant, fetal asphyxia or developmental delay of infant, lower likelihood of breast-feeding and longer hospital stay.<sup>83,90,91</sup> A large Canadian population-based study on composite severe maternal morbidity (defined as haemorrhage requiring hysterectomy or transfusion, uterine rupture, anaesthetic complications, shock, cardiac arrest, acute renal failure, assisted ventilation, venous thromboembolic event, major infection, or in-hospital wound disruption or hematoma), studied morbidity and mortality in healthy women who underwent a planned CD due to breech presentation of the infant.<sup>90</sup> These women were compared to a similar group of women who had planned to deliver vaginally. The authors of the study reported that 2.7% (adjusted OR 3.1, 95% CI 3.0-3.3) of women experienced severe morbidity with planned CD compared to 0.9% with a planned vaginal delivery. Compared to planned vaginal delivery, the group with planned CD had increased risk of cardiac arrest (adjusted OR 5.1, 95% CI 4.1-6.3), wound hematoma (OR 5.1, 95% CI 4.6-5.5), hysterectomy (OR 3.2, 95% CI 2.2-4.8), major puerperal infection (OR 3.0, 95% CI 2.7-3.4), anaesthetic complications (OR 2.3, 95% CI 2.0-2.6), thromboembolism (OR 2.2, 95% CI 1.5-3.2) and haemorrhage requiring hysterectomy (OR 2.1, 95% CI 1.2-3.8). However, the increase of the absolute risks were small. The results were based on an intention-to-treat basis, the planned vaginal delivery group also included unplanned CDs and vaginal instrumental deliveries.<sup>90</sup>

The most serious complication after CD, which however, is very rare in developed countries, is maternal mortality. In confidential enquiries into maternal deaths from the United Kingdom in 2000-2002, the relative risk of maternal mortality after elective and unplanned CD were 2.8 and 4.3 respectively, compared with vaginal delivery.<sup>92</sup> This result could reflect an association between underlying maternal morbidity and the risk of death rather than the CD procedure itself. But many women who deliver vaginally have the same difficulties with an underlying morbidity.<sup>92,93</sup> In the Canadian study mentioned above no mothers died in-hospital in the planned CD group, while in the planned vaginal delivery group 41 women died giving a mortality rate of 1.8 per 100 000 deliveries, though this is a non-significant difference ( $p=0.87$ ).<sup>90</sup> The leading causes of death in the U.S are thromboembolism, haemorrhage and hypertensive disease, whereas thromboembolism and haemorrhage occur more often in CD.<sup>91</sup> It is hard to attribute the exact mortality risk of CD, but estimations suggest a 2-3 times higher risk of maternal death in elective CD and 4 times greater risk in unplanned CD in comparison with vaginal delivery.<sup>91</sup>

In the U.S., wound infections have, been reported to occur in 3% of CDs and may be increasing due to increasing prevalence of obesity. Severe anaesthetic complications (including problems with intubation, aspiration pneumonitis, drug reactions, and complications from high spinals) have a higher incidence in CD (0.29/1000 primary CD) compared to vaginal deliveries (0.06/1000 deliveries). The risk of death from general anaesthesia during CD has decreased over the past 30 years in the U.S from 16.8 to 6.5 deaths per million. However, the risk of death attributed to general anaesthesia during CD is approximately twice as high as death attributed to regional anaesthesia.<sup>91</sup>

Compared with vaginal delivery, CD is associated with higher rates of postpartum haemorrhage (defined by WHO as  $\geq 500$  mL within 24 hours of birth, severe postpartum haemorrhage  $\geq 1000$  mL<sup>94</sup>) and following risk of blood transfusion or hysterectomy. Hysterectomy is reported to occur in 0.2-5/1000 births and is associated with CD. The risk is 10-20-fold higher in CD compared with vaginal deliveries.<sup>91</sup>

Other surgical complications include bowel or bladder injury, postoperative ileus, amniotic fluid embolism, air embolism, thromboembolic disease and maternal death.<sup>91</sup>

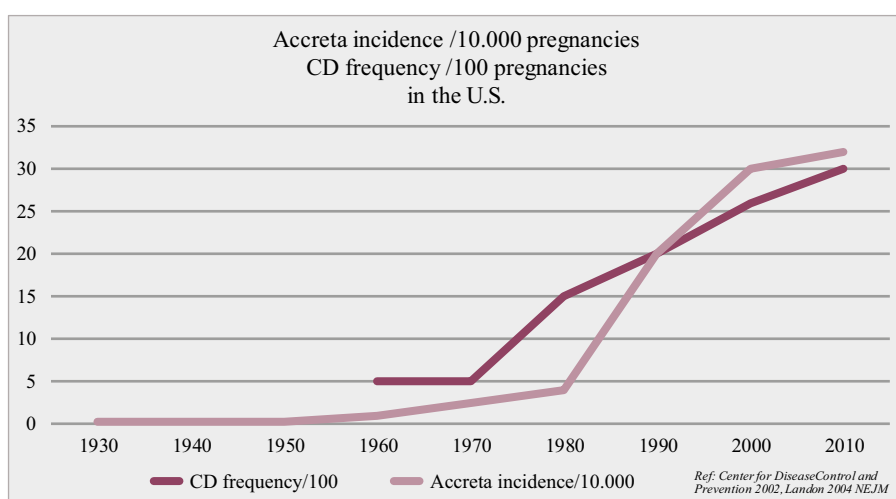
However, a vaginal delivery is also not free from risks. Approximately 10% of all women delivering vaginally encounter some form of complication.<sup>90</sup> Vaginal delivery is associated with increased risk of third- and fourth-degree perineal tears with its long term risk of faecal incontinence. Moreover, studies show that vaginal delivery is associated with an increased risk of urinary incontinence compared to CDs. But it is unclear if this association is explaining the long term persistence of incontinence, or if there are other factors (age, obesity, parity) that contribute to the dysfunction of the pelvic floor.<sup>91</sup>

### **3.4.2 Long term risks**

Uterine rupture is a feared complication and appears mostly during labour in women who have previously had an operation performed on their uterus. After one uncomplicated CD, the risk of rupture was in a study from U.S. 0.5-0.7% in a subsequent delivery.<sup>95</sup> In a Swedish study by Hesselman et al., the uterine rupture incidence was 1.3% in women performing a trial of labour after one previous CD.<sup>96</sup> To avoid the risk of uterine rupture including the risk of maternal and neonatal mortality and morbidity, many clinicians and women in developed countries demand for a repeat CD.<sup>97</sup> In the U.S, 92% of women with one previous CD have a repeat one.<sup>54</sup> Hence, one of the greatest risks of a CD is a repeat CD. Risk factors for uterine rupture are more than one previous CD or CD with incision methods such as classical-, inverted T- or J-incision or other surgical procedures involving the endometrium (myomectomy).<sup>97</sup> Generally, a planned CD is recommended in

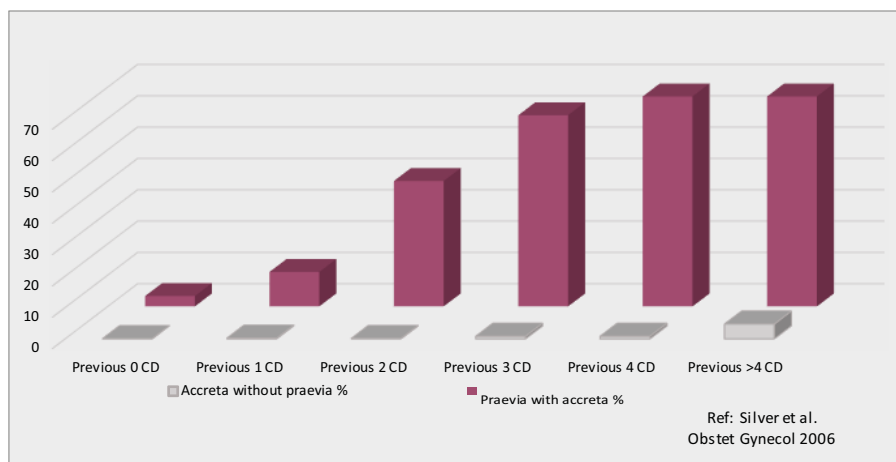
these situations. Maternal characteristics increasing the risk for rupture are obesity, age above 35 and an inter-delivery interval of less than 18 months.<sup>49, 54, 95, 97</sup>

The risk of abnormal placentation (praevia and/or invasive placenta) increases with number of previous CDs. Invasive placenta with placenta accreta, increta and percreta is defined as the trophoblastic attachment, an invasion into the myometrium, invasion through the myometrium and serosa respectively. As seen in Figure 3.5 the incidence of invasive placenta has been increasing as a result of the increasing numbers of CDs over the last decades. Incidence of invasive placenta varies among different reports but the range is between 1 in 300-533 pregnancies in the U.S.<sup>81, 98</sup> According to a Nordic study the incidence of invasive placenta so severe that the women had to have a laparotomy was 3-4 cases in 10,000 deliveries.<sup>82</sup>



**Figure 3.5.** CD and Accreta incidence in U.S

A large multicentre cohort study has shown that the risk of invasive placenta increases with the number of previous CDs. The risk was even greater for women with placenta praevia and a previous CD. As shown in Figure 3.6, women with placenta praevia ran a 3%, 11%, 40%, 61% and 67% risk of invasive placentation at the first, second, third, fourth and fifth or more CDs, respectively. The rate of invasive placenta also increases with increasing CDs without placenta praevia.<sup>99</sup>



**Figure 3.6.** Proportion of invasive placentation with or without placenta praevia and previous CD

Invasive placenta is associated with considerable maternal and fetal morbidity and mortality. The maternal complications are major massive haemorrhaging that can lead to coagulopathy, multi-organ failure, hysterectomy, thromboembolism and even death. The neonatal complications are mainly coupled with preterm birth. With invasive placenta, as with all placental complications, it is crucial to have a correct and accurate prenatal diagnosis. When invasive placenta has been correctly diagnosed, prenatal health care providers can plan for deliveries in a multi-disciplinary way for individualised treatment. This usually involves a planned CD with hysterectomy.<sup>81, 98, 100</sup>

A CD is, as mentioned above, associated with increased risk of abnormal placentation including placenta praevia, but also a risk of placental abruption (ablatio), both of which potentially impact the health of the next infant. CD has also been associated with decreased subsequent fertility, increased likelihood of ectopic pregnancy or miscarriage. Increased complications during next pregnancy and labour including malpresentation, prolonged labour, emergency CD, uterine rupture, preterm birth, low birth weight, small for gestational age and stillbirth have also been reported. However, neither is vaginal delivery without complications, but maternal and neonatal mortality is increased in caesarean that has followed labour, when compared with vaginal delivery or elective CD.<sup>91, 101</sup>

Finally, there is also a risk of abdominal adhesions after a CD. A Swedish study by Hesselmann et al. reported an increased incidence of adhesions after previous CD (37%) in women undergoing later abdominal surgery, compared to women with no previous CD (10%). Adhesions also increased with the number of CDs: 32% after one CD; 42% after two CDs; 59% after three or more CDs (p-value <0.001).<sup>102</sup>

### 3.5 Neonatal risks with caesarean delivery

Caesarean delivery is associated with short-term risks such as asphyxia due to hypoperfusion of the uterus during conduction anaesthesia, scalpel lacerations and neonatal respiratory morbidity (from transient tachypnea of the newborn to severe respiratory distress syndrome) which require neonatal intensive care.<sup>91</sup> Studies suggest a gestational age-dependent incidence of neonatal respiratory morbidity in infants born by CD compared with vaginal birth<sup>103</sup>, and therefore since a couple of years in many countries, it is recommended that elective CD is performed after 39 full gestational weeks. Labour also appears to have a protective effect on neonatal respiratory morbidity, as this morbidity is more present in infants born with CD before the onset of labour, compared with infants born with CD that has followed labour (3.5% versus 1.2%; OR 2.9, 95% CI 1.9-4.4).<sup>91, 103</sup> CD is associated with altered stress response in the newborn infant. There are also studies stating that CD can have long-term immunologic implications on the infant and that the colonization of the gut flora is different in infants born by CD. Thereto longitudinal data that suggests that CD is associated with an increased incidence of asthma, food allergy and atopy and decreased rates of breast-feeding.<sup>49, 91, 103</sup>

Naturally there are also risks when being born by a vaginal delivery, this normally includes birth trauma such as shoulder dystocia and its concomitant sequela, asphyxia from delay in delivery, and injuries due to manipulations used to deliver the infant (i.e. brachial plexus injury). In a review from U.S., shoulder dystocia occurred in 0.2-2.0% of vaginal deliveries, and brachial plexus injuries occurred in 10-20% of all shoulder dystocia cases. Long-term sequela from brachial injuries occurred in 1-2 /10,000 births.<sup>91</sup>

## 4 TRIAL OF LABOUR AFTER CAESAREAN

### 4.1 Background

Today, a trial of labour after one caesarean (TOLAC) is recommended in many countries and considered safe for both the woman and infant. The purpose of this is to limit the escalating CD rates and associated maternal morbidity.<sup>52, 97, 104</sup> In a multicenter study, Landon et al. compared maternal and perinatal outcomes in more than 30,000 women undergoing TOLAC (n=17,898) or having an elective repeat caesarean delivery (ERCD) (n=15,801) before onset of labour.<sup>95</sup> Uterine rupture occurred in 124 (0.7%) women in the TOLAC group and hypoxic-ischemic encephalopathy occurred only in infants whose mother was in the TOLAC group. In the case of 7 of the 12 infants who were affected, this followed a uterine rupture and the figure included 2 neonatal deaths. The rate of endometritis (2.9% vs 1.8%) and blood transfusion (1.7% vs 1.0%) was higher in women undergoing TOLAC, however hysterectomy (0.2% vs 0.3%) and maternal death (0.02% vs 0.04%) did not differ significantly between the groups.<sup>95</sup>

A vaginal birth after a caesarean (VBAC) is associated with fewer complications compared with ERCD.<sup>52, 53, 97</sup> However, a TOLAC which ends with a repeat CD entails higher risks for complications, as described above, than ERCD.<sup>52, 97, 105</sup> Women with a previous caesarean ought to be reviewed in the next pregnancy in order for any contraindications for a TOLAC (e.g. previous uterine rupture, type of previous uterine incision, previous uterine surgery, placenta praevia) to be recognised.<sup>97</sup> Previous investigations show that the likelihood of VBAC ranges between 60 and 80% in different settings and is influenced by both demographic characteristics, such as maternal age, maternal body mass index and weight gain during pregnancy, maternal medical illness and obstetric history, such as indication for first caesarean.<sup>106, 107</sup> In addition, studies have reported a relationship between cervical dilation in the first labour and VBAC rates. These relatively few previous studies are limited by study size, provide contradictory results, and may include multiparous women with previous vaginal and caesarean deliveries, making it difficult to assess the risk of repeat CD.<sup>108-116</sup>

A large study by Hoskins and Gomez found that women who were fully dilated at the first CD only had 13% success rate of VBAC in the subsequent delivery.<sup>108</sup> Furthermore, Kwon et al. reported that the degree of cervical dilation in women with previous labour dystocia did not affect the mode of delivery in a subsequent trial of labour.<sup>110</sup> However, four other studies convincingly have shown that degree of cervical dilation in the first delivery does matter in the subsequent delivery, even when the indication for the first CD was labour dystocia (Table 4.1).<sup>109, 111, 112, 116</sup> Many of these studies include women with a previous vaginal and caesarean delivery, and since previous vaginal delivery is strongly associated with TOLAC

success<sup>117</sup>, interpretation and compare these with primiparous women may be difficult. Further, most previous studies are based on a single hospital or medical centre and local practices in TOLAC, and this is most likely to have affected the results and their generalisability. There is a lack of population-based studies with high granularity for maternal and obstetrical characteristics to further elucidate how obstetric historical factors influence the chance of successful TOLAC and to provide further knowledge when counselling women on safe birth after a first caesarean.

**Table 4.1.** Part of table 3 from Lewkowitz et al.<sup>112</sup> Summary of previous studies on women performing TOLAC with previous CD due to labour dystocia.

Reference	Year	Total study population, n	VBAC rate after prior CD for first stage dystocia, n (%)	VBAC rate after prior CD for second-stage dystocia, n (%)
Hoskins and Gomez <sup>108</sup>	1997	1,533	885/1,288 (69%)	32/245 (13%)
Bujold and Gauthier <sup>109</sup>	2001	859	429/654 (66%)	161/214 (75%)
Kwon et al <sup>110</sup>	2009	380	260/326 (80%)	41/54 (76%)
Abildgaard et al <sup>111</sup>	2013	355	100/115 (47%)	85/140 (61%)
Lewkowitz et al <sup>112</sup>	2015	238	59/132 (45%)	58/106 (55%)
Duff et al <sup>113</sup>	1988	131	78/114 (68%)	11/17 (65%)
Melamed et al <sup>a114</sup>	2013	93	—	57/93 (61%)
Ollendorf et al <sup>115</sup>	1988	88	37/53 (70%)	24/35 (69%)
Impey and O'Herlihy <sup>116</sup>	1988	40	16/25 (64%)	11/15 (73%)

<sup>a</sup> Only women with history of failed operative vaginal delivery who attempted TOLAC

## 4.2 Induction of labour after previous caesarean delivery

In the large multicentre study by Landon et al., with 33,699 women undergoing TOLAC, augmentation with oxytocin or the induction of labour were both associated with increased risk of uterine rupture compared with spontaneous onset of labour (oxytocin only vs spontaneous onset: 1.1% vs 0.4%, OR 3.01 95% CI 1.66-5.46, prostaglandin with or without oxytocin: 1.4% vs 0.4%, OR 3.95 95% CI 2.01-7.79, mechanical method with or without oxytocin: 0.9% vs 0.4%, OR 2.48 95% CI 1.30-4.75).<sup>95</sup> A sub-analysis of the same data only showed an increase of uterine rupture in induced women with no previous vaginal delivery (1.5% versus 0.8%, p-value=0.02), and the cervical ripeness at admission did not affect the uterine rupture risk.<sup>54</sup> A dose effect could be seen as higher maximum doses of oxytocin resulted in an increasing risk of uterine rupture. In another sub-study of the same population, 67% of women with induced labour and 74% of those



requiring oxytocin augmentation achieved a vaginal birth compared to 81% of women with a spontaneous onset of labour (OR 0.50, 95% CI 0.45-0.55 and OR 0.68, 95% CI 0.62-0.75, respectively).<sup>52, 95, 106</sup>

In a Cochrane review, West et al. conclude that the evidence for which induction method is to be preferred for women with previous CD is inadequate since studies are underpowered and the reported specific outcomes were scarce.<sup>118</sup> In another Cochrane review concerning the choice between an ERCD and induced TOLAC, the conclusion was that both a repeat CD or induction are associated with both benefits and negative consequences. The evidence available today is from observational studies and should therefore be interpreted with caution. Randomised trials are needed to provide more reliable evidence.<sup>119</sup>

### **4.3 Childbirth experience**

Giving birth to a child is an important event in a woman's life. Most women recognize that labour might be difficult in order to achieve a positive outcome for both themselves and the child. However, about 10% of women have a negative birth experience, which possibly affects both her and her family's everyday lives and impairs bonding to the child.<sup>120</sup> Sometimes the impact of a negative birth experience can be long-lasting and even impair future fertility.<sup>121-124</sup> Birth experience is multidimensional and complex. However, known factors that are important and can affect the birth experience are maternal age, fear of childbirth, support from the midwife during delivery, lack of support from the partner, induction of labour, prolonged delivery and the memory of pain, expectations of giving birth, involvement and participation during labour, and surgical procedures.<sup>120, 125-131</sup> The mode of delivery is also an important factor and affects the birth experience. For a first-time mother, having a non-instrumental, vaginal, delivery, is associated with the highest rated birth experience, whereas an unplanned CD is considered to be a worse birth experience.<sup>120, 125, 132, 133</sup>

Knowledge about the woman's birth experience in a subsequent delivery after a CD is scarce. The few previous studies show that after a counselling programme on mode of delivery for women with a previous CD, the birth experience was rated best in women achieving a VBAC.<sup>134-136</sup> However, these studies were done after an intervention programme, were limited by confounding, had small or unrepresentative sampling, mixed parity and included women with a previous vaginal birth as well as premature births, and thereby had limited validity and generalisability.<sup>134-136</sup>

### **4.4 Counselling women prior to delivery**

Counselling pregnant women who had undergone a CD prior to their next delivery may be challenging and delicate. The woman and her health care provider must weigh the risks and benefits of attempting a TOLAC against having an ERCD.

The pregnant woman ought to be first reviewed before she is recommended to undergo a TOLAC. Due to enhanced risk of uterine rupture, one important criteria is that she has only one previous, low, transverse incision.<sup>95</sup> Factors associated with increased risk for uterine rupture are lacking and prediction models to aid women and caregivers have not resulted in sufficient prediction accuracy.<sup>137</sup>

One of the most important known factors for successful TOLAC and achieving a vaginal delivery is a history of previous vaginal delivery.<sup>117</sup> Other factors are that the indication for a previous CD was not labour dystocia, and at the trial of labour there was no need for induction or augmentation with oxytocin, and that there was a great cervical dilation at admission, a BMI of less than 30, Caucasian ethnicity and a young age.<sup>106</sup> Previous studies claim that benefits of a TOLAC only exceed the risk of an ERCD when the probability of VBAC is greater than 60-70%, depending also on the woman's individual preferences.<sup>106, 137</sup> Therefore, predicting the individual probability of VBAC could facilitate the decision-making for a safe birth.

A widely used model for predicting VBAC is developed by Grobman et al. and is based on multivariable logistic regression. It was developed to take into account factors present at the first antenatal visit in pregnancies after CD (maternal age, BMI, ethnicity, prior vaginal delivery, the occurrence of a VBAC, and a potentially recurrent indication for the CD).<sup>138</sup> This model was further developed with even better prediction rates, taking into account both factors available at the woman's first antenatal visit and factors that develop as the pregnancy proceeds (developing preeclampsia, cervical status at admission for delivery, BMI at or within 2 weeks of delivery and the undertaking of labour induction). The area under the receiver-operating characteristics curve (AUROC) which is often used to compare tests for predicting, was 0.774 (95% CI 0.764-0.784) for this model. A fair test is said to have an area roughly between 0.70-0.80. An internal validation of the model by Grobman et al. showed the predicted probability of VBAC success corresponded closely with the actual probability for the women in the study.<sup>54, 138</sup> Grobman's model was modified and evaluated by Fagerberg et al. to suit a Swedish setting.<sup>139</sup> Both these models included women with previous vaginal delivery, which is one of the strongest predictors for VBAC.<sup>106, 117</sup> There are, to my knowledge, no models primarily developed for predicting VBAC in women without a previous vaginal delivery, and whose delivery mode is more unpredictable for clinicians.

Today, the availability of data in health care is growing making it easier to use machine learning methods with their ability to consider many candidate predictors and which take into account complex relationships (non-linearity, other complex interactions) as prediction tools.<sup>140-144</sup> These algorithms sometimes even includes predictors that clinicians might not have considered and the results may improve counselling if accuracy is high.<sup>145-148</sup>

A study in 2014 by Kominiarek et al. which used a machine learning method based on classification and regression tree analysis (CART) showed that cervical dilation on admission followed by BMI, were the two most important variables for CD in nulliparas. The CART model makes a progressive dividing of the study population into subgroups according to the variables, and the mathematical model chose the strong predictive variables and tree-like order in which splitting occurs.<sup>147</sup> However, this hierarchical tree-building process can result in a model with low prediction accuracy, and therefore an improvement was developed by Breiman (2001), a “random forest” procedure. This procedure averages multiple regression trees, where from which the machine can detect and account for higher-order interactions as well as non-linear relationships. A disadvantage of this model can be difficulties in interpretation.<sup>149</sup>

Yee et al. studied the relationship between the obstetrician’s cognitive and affective traits and the delivery outcomes among women eligible for TOLAC. They concluded that there was an increased likelihood of going into a TOLAC and succeeding with a VBAC if the obstetrician had more proactive strategy and displayed less anxiety.<sup>150</sup> In another study they concluded that 83% of women with a previous CD had a preference for vaginal delivery and that they could accept a 59% risk of an unplanned repeat CD when undergoing TOLAC instead of choosing ERCD.<sup>151</sup>

Deciding whether to undergo a TOLAC or choose ERCD is complex and difficult and experiences after the first CD strongly influence the woman’s choice for next birth. Shorten et al. showed that for women that chose an ERCD, the risk with TOLAC and potential uterine rupture outweighed the desire of vaginal birth. Women who chose TOLAC seemed more confident in their body and valued vaginal delivery for both the child and for themselves. After the delivery, both groups seemed satisfied with their choice but the women who chose TOLAC and then had to undergo a repeat CD were the least satisfied in comparison with women giving birth vaginally or by an ERCD. The health care providers and the health care system and culture in which the birth took place had strong impact on the woman’s choice.<sup>152</sup>

In a lifetime cost-effectiveness study in the U.S, Gilbert et al. studied the cost-effectiveness of a TOLAC compared with ERCD, including long-term outcomes for both the mother and child, and used the results to determine the future health and economic consequences of the different delivery modes. The study team concluded that when the probability of uterine rupture was 0.8%, TOLAC was less expensive and more effective than ERCD, as long as the probability of TOLAC success was 47% or more.<sup>153</sup>

## 5 AIM

The overall aim of the project was to increase knowledge about delivery in women who had undergone one previous delivery, a caesarean. To study associations between subsequent modes of delivery with the indication of the first caesarean, the risk of a repeat caesarean and the risk of a negative birth experience. Thereto to develop machine learning models to predict vaginal birth after a previous caesarean. Since indications for labour induction are strongly related to indications for caesarean delivery and about 20-40% of induced nulliparous women deliver by caesarean procedure, we also wanted to study the benefits and risks associated with different methods used for labour induction.

The specific aims were to:

- Study time-to-delivery and associated differences of risk (maternal and neonatal morbidity) with different methods for labour induction in nulliparous women with unripe cervix. **(Study I)**
- Study the risk of repeat caesarean delivery during a trial of labour after a caesarean in women with only one previous delivery. **(Study II)**
- Identify the association between delivery mode and the risk of a negative birth experience in women with only one previous delivery, a caesarean. **(Study III)**
- Develop new machine learning models and compare them with two earlier models used for predicting vaginal delivery in women with one previous delivery, who undergoes a trial of labour after caesarean. **(Study IV)**

## **6 MATERIAL AND METHODS**

### **6.1 Setting**

All Swedish citizens, as well as people who have immigrated and have lived in Sweden for longer than one year have their own, unique personal identification number. This was introduced in 1947 and is used in the health care system, for medical records, school systems and for paying taxes. A newborn infant is given this personal identification number directly after birth.<sup>154</sup> Together with the nationwide registers and the structure of the health care system, this, provides a unique possibility for epidemiological research.

All pregnant women have been offered free antenatal care in Sweden for over 50 years now, and the insurance system does not influence the availability of this care. More than 98% of pregnant women participate in the antenatal care system and more than 99% of all births take place in hospitals. Normal pregnancies and deliveries are taken care of by licenced midwives with little involvement from obstetricians, while complicated pregnancies and deliveries are attended by obstetricians. Since the middle of 1980s almost all pregnant women are offered a routine ultrasound scan before the 20th gestational week to assess gestational age and multiple pregnancy as well as for screening for malformations. This ultrasound scan is performed on more than 97% of all women.<sup>12, 76</sup>

### **6.2 Data sources**

#### **6.2.1 The Stockholm-Gotland Obstetric Cohort**

The population-based Stockholm-Gotland Obstetric Cohort<sup>155</sup> includes all births between January 1<sup>st</sup>, 2008 and October 31<sup>st</sup>, 2014 at seven hospitals (n = 175,522) in the Counties of Stockholm (SLL) and Gotland. Some 25,000 to 30,000 deliveries take place in the region each year, accounting for about 25% of all annual deliveries in Sweden. Pregnancy and delivery related data is forwarded from the electronic medical records system (Obstetrix, Cerner Inc., Stockholm, Sweden) used at all antenatal, ultrasound, delivery and postnatal care units in the region. Maternal and infant information for each pregnancy from prenatal care, delivery (including Bishop Score and partograph data) and the postpartum period are entered prospectively into the medical records by midwives and physicians in a standardised way. Detailed information about operative interventions, umbilical cord blood tests and examination of the new-born infant is included in the electronic medical record. This database was established at the Division of Clinical Epidemiology at Karolinska Institutet and funded by the Swedish Research Council.

6.2.2 The Swedish Pregnancy Register

The Swedish Pregnancy Register began in 2013 and is a merge of the Swedish Maternal Health Care Register (established 1999) and the Prenatal Diagnosis Register (established 2010). Today the register covers 98.5% of all births in Sweden and has detailed information about antenatal care including ultrasound examinations, delivery and postnatal care. Data from pregnant women are entered prospectively into the electronic medical records on the first antenatal visit and every subsequent visit, ultrasound examination and at delivery and postnatal care. The Pregnancy Register facilitates improvement in the quality of care as a clinic can benchmark its performance over time, in comparison with other clinics, regions and the nation (Figure 6.1). Data from the Pregnancy Register is used for quality improvement, health care development and after ethical approval, may also be used for research.



Figure 6.1. Example of “dash-board” view of all registered primiparous women in Sweden at or beyond term undergoing a TOLAC ending with a repeat CD, year 2018, The Swedish Pregnancy Register

## 6.3 Study populations and study designs

### 6.3.1 Study I

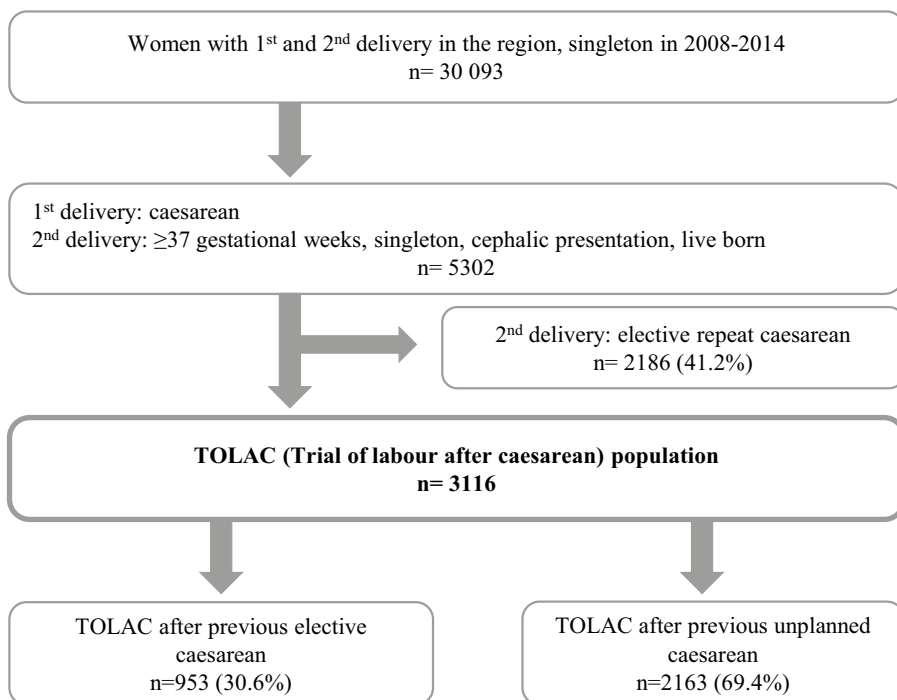
**Study I** is a population-based cohort study with a **study population** from the Stockholm-Gotland Obstetric Cohort. This study comprised all nulliparous women with a singleton, live-born infant in cephalic presentation at or beyond 37 completed gestational weeks with induced labour. Women registered with more than one first induction method or with a Bishop Score 7 or more were excluded. Incomplete Bishop Scores were considered as missing.

The **exposure** in **Study I** was labour induction method; (a) prostaglandin E2 (dino-prostone gel or vaginal pessary), (b) orally administered synthetic prostaglandin E1-analogue, misoprostol or (c) transcervical single balloon catheter. If more than one method was used we considered the first method of choice as exposure according to intention-to-treat.

**Primary outcome** of **Study I** was time-to-delivery, identified in the electronic labour records and defined as hours from the start of induction that is from the placement of the balloon catheter or the administration of the initial prostaglandin dose, to birth. **Secondary outcomes** were mode-of-delivery, maternal complications based on the International Classification of Diseases, 10th revision (ICD-10) defined as; (a) fever during delivery (temperature above 38.5 °C); (b) infections (including chorioamnionitis, endometritis, sepsis, urinary-, genital tract-and wound infection or other specified infections); (c) postpartum haemorrhage (estimated blood loss  $\geq 1000$  ml); (d) anal sphincter injury grade 3-4 (only vaginal births included) and (e) urinary retention (defined as  $>1000$  ml at catheterization or post void residual bladder volume  $>300$  ml). Neonatal outcomes included Apgar score of  $<4$  or  $<7$  at 5 min, metabolic acidosis defined as umbilical arterial pH  $<7.10$  and base excess (BE)  $<-12$  or only pH  $<7.0$  and compound asphyxia (metabolic acidosis or Apgar  $<7$  at 5 min).

### 6.3.2 Studies II and IV

**Studies II** and **IV** are population-based cohort studies with the **study population** from the Stockholm-Gotland Obstetric Cohort.<sup>155</sup> We extracted information from the cohort on all women with a first and second singleton delivery during the study period between 2008 and 2014. We then selected all women with a second delivery with singleton, live-born infants in cephalic presentation at 37 or more completed gestational weeks who underwent a caesarean section at first delivery. All women who had an ERCD were excluded, thus only women undergoing TOLAC were included in the final study cohort (Figure 6.2).



**Figure 6.2.** Flowchart of the population in study II and IV, women with first and second delivery between 2008 and 2014

Indication for first CD was the main **exposure** in **Study II** and was categorised into; 1) elective indication (reference) and 2) unplanned CD; a) labour dystocia, b) non-reassuring fetal well-being, c) other indications (e.g. preeclampsia and diabetes). Women, with a planned elective first CD, who came to the delivery ward with contractions or rupture of the membranes and whose vaginal cervical examination showed a cervical dilation greater than 2 cm, were categorised into “other indications”. Cervical dilation at the time of first CD in women with labour dystocia was categorised into:  $\leq 5$  cm, 6-10 cm and fully dilated. Women who underwent a first elective CD were assumed to have no cervical dilation at the time of the caesarean and were used as the reference category. In **Study II** the main **outcome** was risk of a repeated CD.

In **Study IV**, we studied the same population of women as in Study II, our **aim was to predict vaginal birth** in the second delivery in women with only one previous delivery, a caesarean delivery. We wanted to support clinical counselling before labour onset, so the temporal point of prediction was set between 35 and 38 full gestational weeks. We included demographic and social variables from both



first and second pregnancies, variables related to the first pregnancy and CD, and information about first infant, pre-gestational health conditions, and conditions that developed during both pregnancies and information about each delivery hospital. We also included sex of the second infant. Intended onset of labour was also included, since this is important for a successful TOLAC.<sup>106</sup>

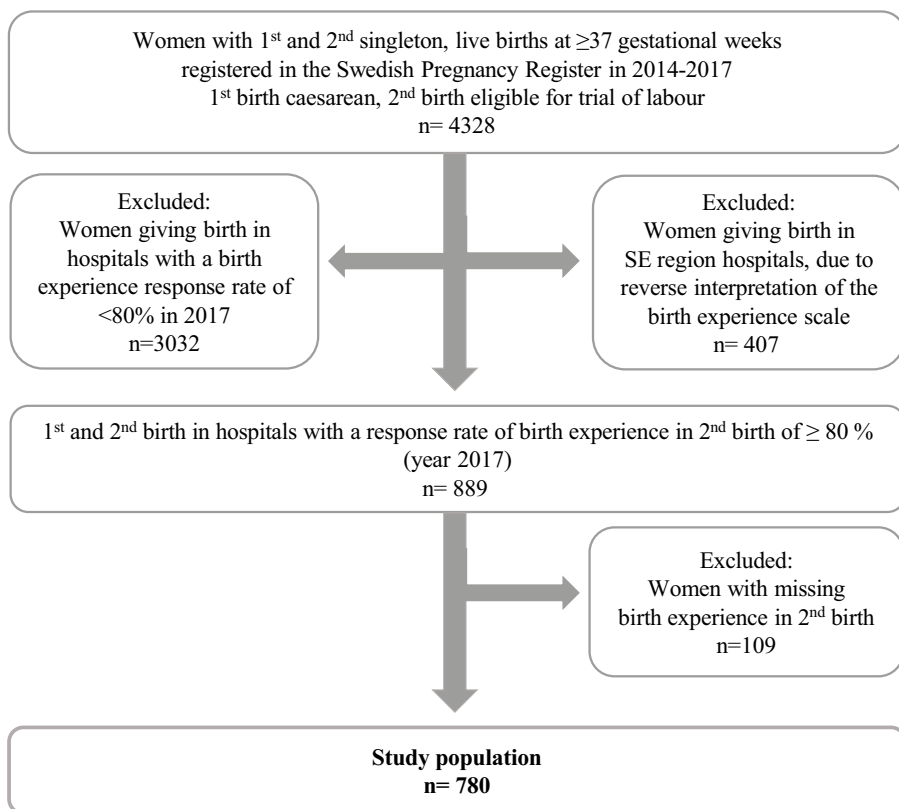
We used three machine learning methods (conditional inference tree, conditional random forest, and lasso binary regression) to develop an individualised prediction model. We compared the new models with two previously existing models by Grobman et al.<sup>158</sup> and by Fagerberg et al.<sup>139</sup>, we measured area under the receiver-operating curve (AUROC), overall accuracy, sensitivity, specificity and calibration.

### 6.3.3 Study III

**Study III** is a population-based cohort study with a **study population** from the Swedish Pregnancy Register.<sup>157</sup> In this study, we collected information on all women registered in the Swedish Pregnancy Register with a first caesarean delivery and a subsequent birth of a singleton, live-born infant in cephalic presentation at 37 or more completed gestational weeks during the years 2014-2017.

In many hospitals in Sweden, after delivery and before discharge from the delivery unit, women are asked about their childbirth experience. The visual analogue scale (VAS) scoring from 1 to 10, where 10 is a very positive and 1 is a very negative birth experience is used for this. The VAS scores are prospectively entered in the electronic medical records by the responsible midwife and forwarded into the Swedish Pregnancy Register. The preliminary analysis showed that some regions had lower rate of reporting birth experience, possibly due to differences in how the care was organized, although response rates did however increase over time. To diminish confounding resulting from organizational factors and to increase internal validity, we excluded women giving birth in hospitals with a birth experience response rate of less than 80% in 2017 (23 hospitals excluded). Until 2017, seven hospitals in the south-east region had the opposite interpretation of the VAS score, and we also excluded these hospitals. And finally, we excluded births where birth experience data was missing, giving us a final population of 780 women with a first and second birth in any of the remaining 12 hospitals (Figure 6.3).

The main **exposure** in **Study III** was mode of delivery for the 2<sup>nd</sup> birth, categorised into elective repeat caesarean delivery (ERCD), vaginal birth after caesarean (VBAC) or unplanned repeat caesarean delivery (CD). Women with an ERCD were used as a reference. Further categorisation was made when studying 1<sup>st</sup> and 2<sup>nd</sup> mode of delivery and its association with the outcome, 1<sup>st</sup> delivery was either elective CD or unplanned CD. Here women with an elective CD in both their 1<sup>st</sup> and 2<sup>nd</sup> births were used as reference.



**Figure 6.3.** Flowchart of the population in study III

The main **Outcome** of **Study III** was the mean birth experience VAS score. Previous studies have shown that about 10% of women assessed their birth experience as negative.<sup>120, 159</sup> In our study, 78 women (10% of 780) scored their birth experience as 5 or lower, and therefore a negative birth experience was defined as VAS score ≤5.

## 6.4 Statistical analyses

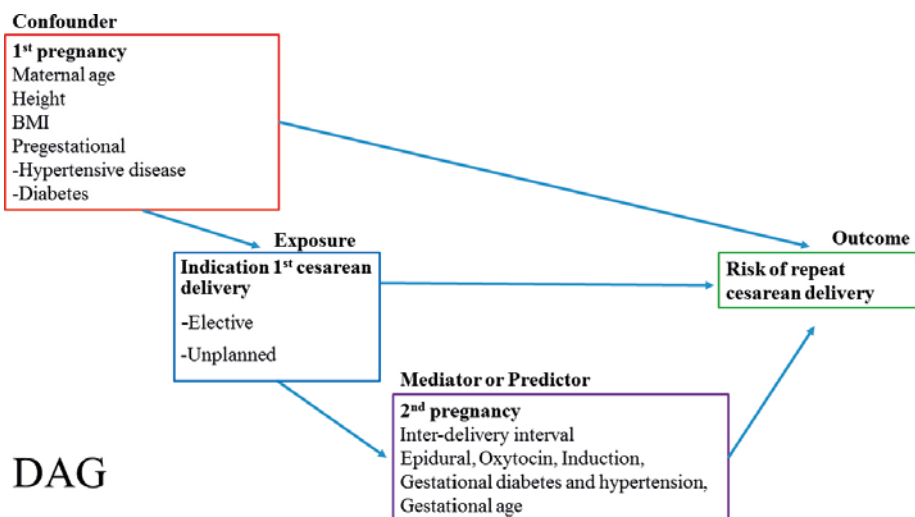
Maternal and delivery characteristics in **Studies I, II and III** were analysed using the Chi-square test for categorical variables and the Student's t-test for continuous variables. A two-sided p-value <0.05 was considered statistically significant.

In **Study I**, crude and adjusted mean time-to-delivery in hours with  $\beta$ -estimates and 95% confidence intervals (95% CI) was calculated by linear regression analysis adjusted for maternal age, height, BMI, year-of-delivery, delivery hos-

pital, gestational age, hypertensive disease and diabetes (Model 1). In Model 2, adjustment for Bishop Score, was added as a continuous variable. Crude and adjusted odds ratios (aOR) with 95% CI were calculated using logistic regression to estimate the association between induction method and delivery within 24h, risk of caesarean delivery, instrumental vaginal delivery, maternal and neonatal complications with the dinoprostone group as a reference. In the adjusted logistic regression model, we adjusted for the same confounders as in the final linear regression model (Model 2). Kaplan-Meier analyses, comparing crude time-to-delivery, were calculated stratified by Bishop Score categories with delivery as the event. A Log-rank test was performed where a P-value of  $<0.05$  was considered as statistically significant. We tested for interaction between induction methods and time to delivery by Bishop Score.

In **Study II** modified Poisson regression analysis was performed to calculate relative risks (RRs), with 95% confidence intervals (95% CI). Adjustments were made for the following confounders after they had been considered through a directed acyclic graph; maternal age, maternal height, body mass index (BMI), maternal pregestational diabetes and pregestational hypertensive disease at first pregnancy (Figure 6.4.). We performed stratified analyses for induction and spontaneous onset of labour and the risk of repeat CD. Finally, we investigated possible effect modification between the induction of second labour and the indication of a first CD associated with a repeat CD. A two-sided p-value  $<0.05$  was considered statistically significant.

When analysing data in **Study III**, linear regression analysis was used to calculate the  $\beta$ -estimates of mean birth experience and logistic regression used for analysing the odds ratio (OR) for negative birth experience. Both were used with 95% confidence intervals (CI). Adjustments were performed for the following confounders; maternal age at 2<sup>nd</sup> birth, BMI, height, and cohabiting at first antenatal visit in the 2<sup>nd</sup> pregnancy, education ( $\leq 9$  years of basic education, secondary school, university or college education), self-assessed health (categorised from very bad to very good) and fear of childbirth in the 2<sup>nd</sup> pregnancy (defined as having the need of extra support from either midwife, obstetrician or psychologist during pregnancy), and birth experience in the 1<sup>st</sup> birth (measured through the VAS score). Additionally, mode of delivery in 1<sup>st</sup> birth (elective or unplanned CD) was included as a confounder. Stratification by 1<sup>st</sup> birth, by 2<sup>nd</sup> mode of delivery with the analysis of mean birth experience and odds of negative birth experience was also performed. We also investigated a possible effect modification between mode of delivery in 1<sup>st</sup> and 2<sup>nd</sup> births associated with birth experience. A sensitivity analysis compared women giving birth in the hospitals included in our study with and without birth experience scores. A two-sided p-value of  $<0.05$  was considered statistically significant.



**Figure 6.4.** Directed acyclic graph (DAG) in study II. The influence of maternal characteristics in 1<sup>st</sup> and 2<sup>nd</sup> pregnancy, and management in 2<sup>nd</sup> delivery, on the association between indication of 1<sup>st</sup> caesarean and risk of repeat caesarean delivery.

In **Study IV**, our general strategy was: 1) Curate the cohort to include all of the applicable variables used in Grobman<sup>138</sup> and Fagerberg<sup>139</sup> models. 2) Divide the cohort into training and validation sets, using a 1:1 split by random sampling. 3) Replace missing data by using single imputation. 4) Predict VBAC in the validation dataset using the estimates reported by Grobman and Fagerberg. 5) Refit the logistic regression models by Grobman and Fagerberg in the training dataset and summarize their performance in the validation dataset. 6) Fit a conditional inference tree<sup>160</sup>, a conditional random forest<sup>161</sup>, and a lasso binary regression model using the training dataset and summarize their performance in the validation dataset.<sup>162</sup> 7) Compare the predictive performance of the new models with that of the Grobman and Fagerberg models. Then a sensitivity analysis was performed by fitting the same new models on the entire (training and validation) dataset and estimating classification error using 5-fold cross validation.<sup>144</sup> For more detailed information, see Paper III. For all models, we calculated AUROC, accuracy, sensitivity, and specificity in the validation dataset, based on a 50% decision cut-off for predicted probability. A calibration plot from the validation dataset for each model was constructed. This plot compares the predicted to observed probability of VBAC and provides a view of model performance across the range of predicted probability.

Analyses in **Studies I, II and III** were conducted by using SAS version 9.4. **Study IV** was analysed by using R version 3.5.1.

**Table 6.1.** Summary of Studies I-IV

	Study I	Study II	Study III	Study IV
<b>Design</b>	Cohort	Cohort	Cohort	Cohort
<b>Data source</b>	Stockholm-Gotland Obstetric Cohort 2008-2014	Stockholm-Gotland Obstetric Cohort 2008-2014	Swedish Pregnancy Register 2014-2017	Stockholm-Gotland Obstetric Cohort 2008-2014
<b>Population</b>	7551 nulliparous women induced	3116 primiparous women undergoing TOLAC	780 primiparous women with a first CD and a subsequent delivery	3116 primiparous women undergoing TOLAC
<b>Exposure</b>	Labour induction method: 1) dinoprostone 2) misoprostol 3) single balloon catheter	Indication for first CD: 1) elective indication 2) labour dystocia 3) non-reassuring fetal well-being 4) other unplanned indications	Mode of 2 <sup>nd</sup> delivery 1) ERCD 2) VBAC 3) unplanned repeat CD	Prediction model: 1) by Grobman et al. 2) by Fagerberg et al. 3) Conditional inference tree 4) Conditional random forest 5) Lasso binary regression
<b>Outcome</b>	Primary: time-to-delivery Secondary: Maternal and Neonatal adverse outcomes	Mode of delivery in 2 <sup>nd</sup> birth  Risk of repeat CD	Birth experience in 2 <sup>nd</sup> birth (visual analogue scale 1-10)  Risk of negative birth experience	Prediction of vaginal birth; 1) area under ROC 2) accuracy 3) sensitivity 4) specificity 5) 5-fold cross validation accuracy
<b>Methods</b>	Linear and logistic regression analysis Kaplan-Meier analysis with log-rank test	Poisson regression analysis	Linear and logistic regression analysis	Imputation of missing variables, regression analysis, conditional inference tree and random forest, lasso binary regression
<b>Confounders/ Predictors</b>	Maternal age, height, BMI, year-of-delivery, delivery hospital, gestational age, hypertensive disease, diabetes, Bishop Score	Maternal age, height, BMI, gestational age, pregestational diabetes and pregestational hypertensive disease at first pregnancy	Maternal age at 2 <sup>nd</sup> birth, BMI, height and cohabiting at 1 <sup>st</sup> antenatal visit in 2 <sup>nd</sup> pregnancy, education, self-assessed health at early 2 <sup>nd</sup> pregnancy, fear of childbirth in 2 <sup>nd</sup> pregnancy, birth experience and mode of delivery in 1 <sup>st</sup> birth	Diagnoses and procedures related to the pregnancy, labour, delivery and postpartum for infant 1 and related to pregnancy for infant 2

## 6.5 Ethical considerations and funding

Ethical research principles are based on and developed from the “Declaration of Helsinki” originally from 1964. These principles are for medical research involving human subjects, including research on identifiable human material and data. One of the most important statements is the following: *“It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.”*<sup>163</sup>

The Personal Data Act aims to protect personal integrity in the processing of personal data. In large population-based studies personal consent from participants is seldom required. In our studies no informed consent was collected, however, no results were presented on an individual level, and all data was anonymous. Important is also to weight the benefits and importance of the gained knowledge against the possible discomfort the studied individuals might experience. According to the Personal Data Act, research can only be conducted if ethical permission is given from one of the six ethical boards in Sweden.

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**Ethical approval for studies I, II and IV:** The regional ethical committee at Karolinska Institutet, Stockholm, Sweden approved the study protocol (No. 2009/275-31 and No. 2012/365-32), dates of approval April 2<sup>nd</sup> 2009 and March 14<sup>th</sup> 2012.

**Ethical approval for study III:** The regional ethical committee at Karolinska Institutet, Stockholm, Sweden approved the study protocol (No. 2017/2385-31/5 and No. 2018/1601-32), dates of approval January 11<sup>th</sup> and March 27<sup>th</sup> 2018.

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## 7 SUMMARY OF RESULTS

### 7.1 Time-to-delivery comparing induction methods (Study I)

In our dataset, 7551 nulliparous women were induced at or beyond term, with a singleton, live-born infant in cephalic presentation, and a Bishop Score below 7. Women induced with dinoprostone were generally older, less likely to smoke and had a more unripe cervix and 25% had an additional induction method (balloon catheter or misoprostol). In women induced with misoprostol, 24% had a second induction method (balloon catheter or dinoprostone), while of the women induced with a balloon catheter only 1% needed an additional induction method (dinoprostone or misoprostol). Furthermore, women induced with a balloon catheter were more likely to have a Bishop Score >2 and received more epidural anaesthesia (79% versus 71-72%) and oxytocin augmentation, compared to women induced with the prostaglandin methods (94% versus 77-78%). The most common indication for labour induction was post-term pregnancy (32%).

In all vaginal deliveries and CDs carried out as a result of labour dystocia or failure of induction, mean-time-to-delivery was in comparison to dinoprostone, 2 h or 10 h shorter when the induction method was with misoprostol or balloon catheter respectively (Model 1). When adjustment for the Bishop Score was also included, mean-time-to-delivery was 1.5 h or 7 h shorter with misoprostol or a balloon catheter as the first induction method. When analyzing all deliveries (all vaginal and all caesarean deliveries), time-to-delivery was overall shorter, but the time-to-delivery relation between the three induction methods was unchanged (Table 7.1).

**Table 7.1.** Time (hours) from induction start to delivery by induction method

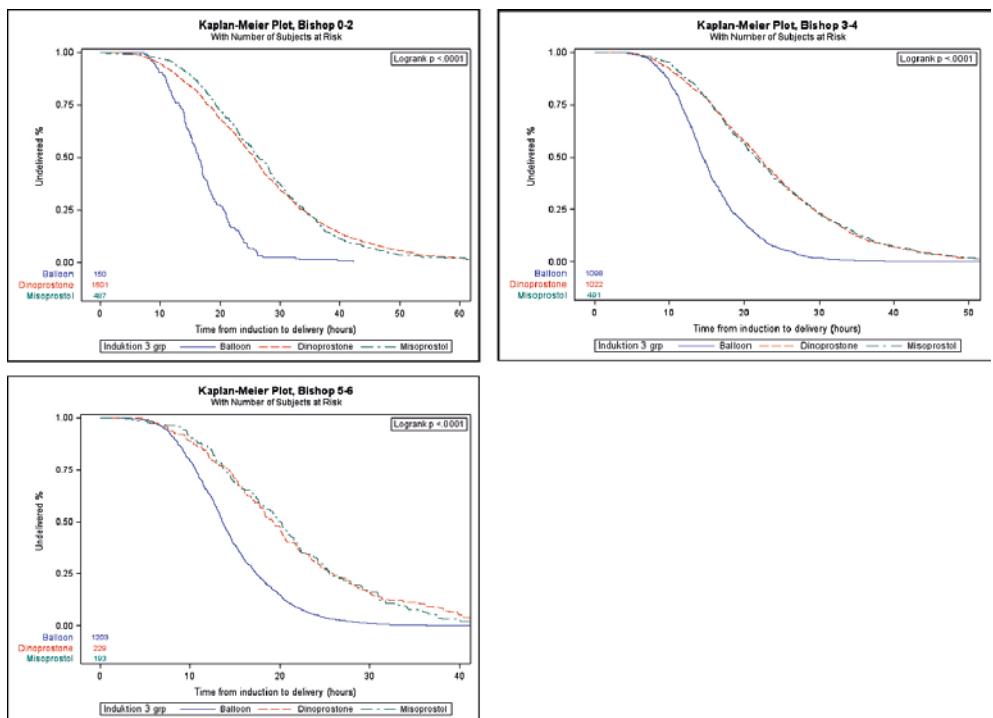
Induction method	Model 1 <sup>1</sup>				Model 2 <sup>2</sup>		
	Crude Mean	Adjusted Mean	β	(95% CI)	Adjusted Mean	β	(95% CI)
<b>Vaginal deliveries and caesarean deliveries due to labour dystocia and induction failure</b>							
Dinoprostone	25.20	25.25	Reference		24.08	Reference	
Misoprostol	24.59	23.08	-2.17	(-2.94 to -1.41)	22.55	-1.53	(-2.29 to -0.77)
Balloon catheter	15.04	15.50	-9.75	(-10.30 to -9.20)	17.16	-6.93	(-7.57 to -6.28)
<b>All deliveries</b>							
Dinoprostone	24.41	24.53	Reference		23.50	Reference	
Misoprostol	24.13	22.55	-1.98	(-2.70 to -1.26)	22.11	-1.39	(-2.11 to -0.67)
Balloon catheter	14.87	15.32	-9.21	(-9.73 to -8.70)	16.80	-6.70	(-7.31 to -6.09)

<sup>1</sup> Model 1: adjusted for maternal age, height, body mass index (BMI), year of delivery, hospital, gestational age, hypertensive disease and diabetes

<sup>2</sup> Model 2: adjusted for maternal age, height, body mass index (BMI), year of delivery, hospital, gestational age, hypertensive disease, diabetes and Bishop Score

We could see that there was an interaction between the Bishop Score and time-to-delivery for balloon catheter versus dinoprostone (p-value <0.0001), but this interaction was not found in misoprostol versus dinoprostone (p-value = 0.76). When stratifying for Bishop Score into three groups (Bishop Score 0-2, 3-4, 5-6) and with Kaplan-Meier analyses including log-rank tests comparing time-to-delivery, there was a significant difference between the three induction methods (p-value <0.0001; Figure 7.1).

When analyzing associations between induction method and maternal and neonatal outcome, we found that 94% of the women induced with a balloon catheter had delivered within 24 h, whereas only 55% and 54% had delivered in the misoprostol and dinoprostone groups respectively. In addition, misoprostol had an association with a 24% increased risk of instrumental vaginal delivery compared to dinoprostone. There were no differences in risk of CD, maternal or neonatal complications in any of the three induction groups (Table 7.2).



**Figure 7.1.** Kaplan-Meier plots of crude time-to-delivery, stratified for Bishop Score  
Mean time:

Bishop Score 0-2: Balloon 17 h, Dinoprostone 27 h, Misoprostol 28 h

Bishop Score 3-4: Balloon 15 h, Dinoprostone 23 h, Misoprostol 23h

Bishop Score 5-6: Balloon 14 h, Dinoprostone 21 h, Misoprostol 21 h



**Table 7.2.** Mode of delivery, maternal complications and neonatal outcomes by induction method

Outcome	Dinoprostone (Reference)			Misoprostol			Balloon catheter		
	n	(%)		n	(%)		n	(%)	aOR <sup>1</sup> (95% CI)
Delivery within 24 h	1771	(53.9)		775	(54.7)	1.42 (1.20-1.67)	2626	(93.5)	7.98 (6.60-9.66)
Caesarean delivery	1197	(36.3)		437	(30.7)	1.05 (0.89-1.24)	844	(29.8)	1.11 (0.97-1.28)
Vacuum or forceps extraction	546	(16.6)		241	(16.9)	1.24 (1.01-1.51)	511	(18.1)	1.15 (0.97-1.36)
Postpartum haemorrhage	491	(14.9)		213	(15.0)	1.00 (0.81-1.24)	403	(14.3)	0.90 (0.75-1.07)
Fever (> 38.5°C) during delivery	141	(4.3)		98	(6.9)	1.19 (0.86-1.64)	136	(4.8)	1.34 (0.99-1.81)
Maternal infectious disease or fever	263	(8.0)		148	(10.4)	1.11 (0.85-1.43)	229	(8.1)	1.26 (1.00-1.59)
Urinary retention	58	(1.8)		34	(2.4)	1.14 (0.67-1.94)	47	(1.7)	0.77 (0.47-1.27)
Sphincter injury <sup>2</sup>	188	(9.0)		88	(8.9)	1.11 (0.81-1.54)	162	(8.2)	1.00 (0.76-1.32)
Apgar score < 7 at 5 min	41	(1.3)		19	(1.3)	1.32 (0.67-2.57)	35	(1.2)	0.88 (0.51-1.54)
Apgar score < 4 at 5 min	7	(0.2)		6	(0.4)	3.79 (0.95-15.16)	4	(0.1)	0.51 (0.13-2.04)
pH < 7.0	17	(0.7)		13	(1.2)	0.92 (0.35-2.42)	12	(0.5)	1.02 (0.40-2.55)
pH < 7.10	136	(5.7)		85	(7.7)	1.06 (0.75-1.51)	105	(4.7)	0.86 (0.62-1.19)
BE < -12	80	(3.4)		50	(4.6)	1.10 (0.71-1.72)	72	(3.2)	0.93 (0.62-1.39)
Metabolic acidosis <sup>3</sup>	65	(2.7)		34	(3.2)	0.92 (0.55-1.56)	49	(2.2)	0.87 (0.55-1.39)
Compound asphyxia <sup>4</sup>	103	(3.1)		51	(3.6)	1.26 (0.83-1.91)	83	(2.9)	0.94 (0.65-1.35)

<sup>1</sup> aOR: adjusted for maternal age, height, body mass index (BMI), year of delivery, hospital, diabetes, hypertensive disease, gestational age and Bishop Score. <sup>2</sup> Vaginal births only. <sup>3</sup> Metabolic acidosis (pH < 7.10 and BE < -12, or pH < 7.0). <sup>4</sup> Compound asphyxia (metabolic acidosis or Apgar < 7 at 5 min)

## 7.2 Risk of repeat CD (study II)

Of the 5302 women eligible for trial of labour after one first CD, 41% had an ERCD, while the remaining 3116 women underwent a TOLAC (Figure 6.2.). Almost 70% of all the women going through a TOLAC had a vaginal birth, with the highest rates of VBAC when the first CD had been elective. When the first CD had been performed due to labour dystocia, the risk for repeated CD was almost double (aRR 1.96, 95% CI 1.69-2.27) compared to an elective first CD. (Table 7.3).

**Table 7.3.** Mode of delivery in 2<sup>nd</sup> birth and risk ratio for repeat caesarean in women with trial of labour after caesarean by indication of and cervical dilatation at 1<sup>st</sup> caesarean delivery

	Mode of delivery in 2 <sup>nd</sup> birth				Risk Ratio for repeat CD			
	Vaginal		Caesarean		Crude		Adjusted <sup>c</sup>	
	n	%	n	%	cRR	95% CI	aRR	95% CI
<b>First caesarean delivery</b>	2146	68.9	970	31.1				
Elective CD <sup>a</sup> (Ref)	756	79.3	197	20.7	1.00		1.00	
Unplanned CD	1390	64.3	773	35.7	1.73	1.51-1.98	1.64	1.43-1.89
<b>Indications for unplanned CD</b>								
Labour dystocia	550	56.2	429	43.8	2.12	1.84-2.45	1.96	1.69-2.27
NRFBW <sup>b</sup>	535	67.4	259	32.6	1.58	1.35-1.85	1.48	1.26-1.75
Other indications	305	78.2	85	21.8	1.05	0.84-1.32	1.05	0.84-1.32
<b>Cervical dilation when labour dystocia</b>								
≤5 cm	130	45.3	157	54.7	2.65	2.25-3.11	2.48	2.09-2.94
6-10 cm	256	57.5	189	42.5	2.05	1.74-2.42	1.98	1.67-2.35
Fully dilated	157	68.6	72	31.4	1.52	1.21-1.91	1.46	1.15-1.86
Missing	7	-	11	-				

<sup>a</sup> CD: Caesarean delivery, <sup>b</sup> NRFBW: Non reassured fetal well-being, <sup>c</sup>Adjusted for maternal age, height, body mass index (BMI), pregestational diabetes and pregestational hypertensive disease at 1<sup>st</sup> pregnancy

In women with a first labour dystocia, VBAC rates increased with increasing cervical dilation before the first CD as well as the risk for repeat CD decreased, in comparison with women whose first CD had been elective (Table 7.3).

When analysing the risk for repeat CD in association with the onset of second delivery together with the indication for first CD, the risk was highest in women with an induction in second delivery and unplanned first CD indication (aRR 1.97, 95% CI 1.60-2.41) (Table 7.4). However, the possible effect modification by onset of second delivery was statistically significant ( $p=0.03$ ).

**Table 7.4.** Crude and adjusted risk ratio for repeat caesarean delivery in women with TOLAC by indication of first caesarean delivery and onset of second delivery

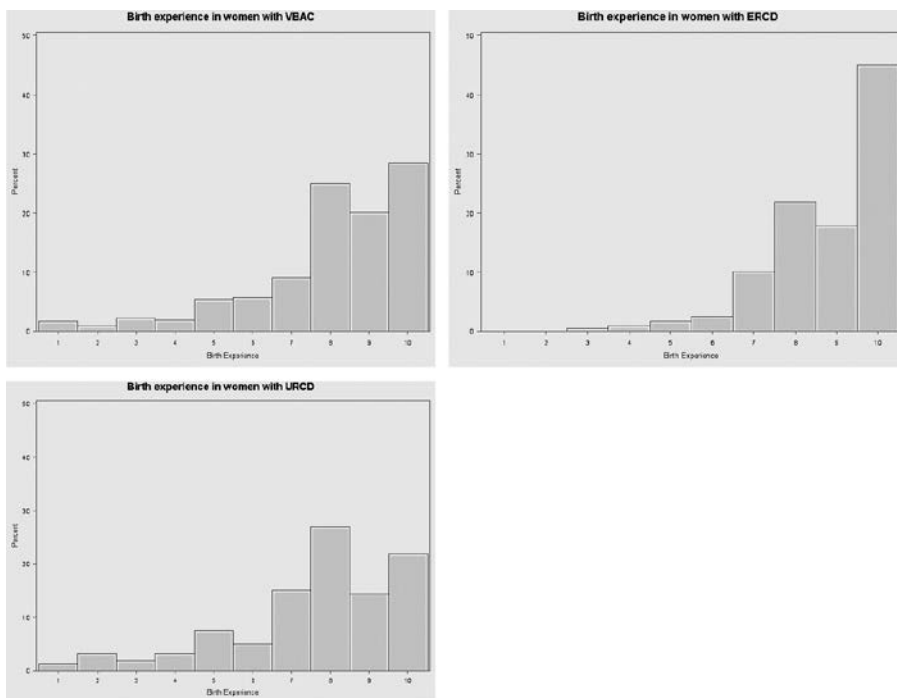
Indication of 1 <sup>st</sup> CD and Onset of 2 <sup>nd</sup> delivery	Repeated CD		Crude risk repeat CD		Adjusted risk <sup>a</sup> repeat CD	
	n	%	cRR	95% CI	aRR	95% CI
Elective indication spontaneous onset (n=747) (Reference)	131	17.5	1.00		1.00	
Unplanned indication spontaneous onset (n=1765)	598	33.9	1.93	1.63-2.29	1.81	1.53-2.14
Elective indication induction (n=206)	66	32.0	1.83	1.42-2.35	1.43	1.10-1.86
Unplanned indication induction (n=398)	175	44.0	2.51	2.07-3.03	1.97	1.60-2.41

<sup>a</sup> Adjusted for maternal age, height, body mass index (BMI), pregestational diabetes and pregestational hypertensive disease at 1<sup>st</sup> pregnancy

### 7.3 Risk of negative childbirth experience (Study III)

Out of the 780 women included in our study, 68% went through a trial of labour and 32% had an ERCD. Women in the ERCD group were older, had a higher level of education, their gestational age was lower and more feared childbirth in comparison with the TOLAC group. Of the women performing TOLAC, 70% had a vaginal birth (VBAC) and 30% had an unplanned repeat CD. Compared to the unplanned repeat CD group, women who succeeded with a VBAC were younger, taller, had a lower BMI, were more often cohabiting with the infant's father and were non-smokers. Moreover, fewer were induced and the prevalence of fear of childbirth was lower.

The distribution of the rating of the birth experience for women giving birth a second time was skewed towards the higher numbers (Figure 7.2). More than 60% of all women scored a birth experience of 8 or more, independently of mode of delivery for the 2<sup>nd</sup> birth. The mean birth experience in women with an ERCD was 8.8. After adjustment, women with a VBAC and unplanned repeat CD had a, 0.5 (95% CI; -0.9 to -0.01) and 0.9 (95% CI; -1.5 to -0.3) lower mean difference of birth experience compared with women with an ERCD.



**Figure 7.2.** Histogram of birth experience after 2<sup>nd</sup> birth by mode of delivery in 2<sup>nd</sup> birth; Elective repeat caesarean delivery (ERCD), vaginal birth after caesarean (VBAC) and unplanned repeat caesarean delivery (URCD)

After adjusting for confounders, women giving birth by unplanned repeat CD had a five-fold increased risk of a negative birth experience (aOR 5.1, 95% CI; 1.5 to 16.7) in comparison with women undergoing ERCD (Table 7.5). When stratifying for first birth, women with a first and a second unplanned CD were at greatest risk of a negative birth experience (crude OR 9.2, 95% CI; 2.1 to 40.0) in comparison with women with a first and a second elective CD.

**Table 7.5.** Odds of negative birth experience by mode of delivery in 2<sup>nd</sup> birth, logistic regression

Mode of delivery in 2 <sup>nd</sup> birth**	Negative birth experience 2 <sup>nd</sup> birth							
	Crude n	%	OR	95% CI	Model 1* aOR	95% CI	Model 2* aOR	95% CI
<b>ERCD</b>	7	2.8	Reference		Reference		Reference	
<b>VBAC</b>	44	11.8	4.6	2.0-10.4	4.5	1.7-11.9	2.3	0.7-7.3
<b>URCD</b>	27	16.9	7.0	3.0-16.4	7.4	2.7-20.3	5.1	1.5-16.7

\* Adjustment in

Model 1: maternal age, height, BMI, cohabiting, education, self-assessed health in 2<sup>nd</sup> pregnancy

Model 2: same as in Model 1 and fear of childbirth in 2<sup>nd</sup> pregnancy, birth experience after 1<sup>st</sup> birth and mode of delivery in 1<sup>st</sup> birth (elective vs unplanned CD)

\*\*ERCD (elective repeat caesarean delivery), VBAC (vaginal birth after caesarean), URCD (unplanned repeat caesarean delivery)

## 7.4 Prediction of VBAC (Study IV)

As in study II, of the 5302 women with a first CD and a subsequent delivery, 41% had an elective repeat CD. The remaining 3116 women performed a TOLAC, of whom 2146 women (69%) gave birth vaginally (VBAC) and 970 had an unplanned repeat CD (31%) (Figure 6.2).

Women delivering vaginally were more likely to be younger, taller, have a lower BMI and a lower change in BMI from the first to second pregnancy. They were more likely to deliver in a hospital with lower rate of unplanned CDs and have a spontaneous labour onset in the second delivery. Their second infant were more likely to be female. These women were less likely to have had labour dystocia as the indication of the first CD and were more likely to have had a spontaneous onset of first delivery and have reached second stage of labour before the CD or have an elective indication for the first CD. Further, they were more likely to have a lower gestational age, a smaller infant, and a shorter length of stay in the hospital after the first delivery, They were also less likely to have had a puerperal or postpartum infection in first delivery, and less likely to suffer from any hypertensive disorder in second pregnancy or any endocrine or lung disease at all.

AUROC ranged from 0.61 to 0.69, sensitivity was above 91% and specificity (the probability of correctly identifying a repeat CD) below 22% for all models (Table 7.6). In the validation dataset, the conditional inference tree assigned to every woman a probability of VBAC to >50%, giving a 100% sensitivity and 0% specificity. Accuracy (correctly classified delivery modes) ranged from 68% to 70%, 5-fold cross-validation was similar.

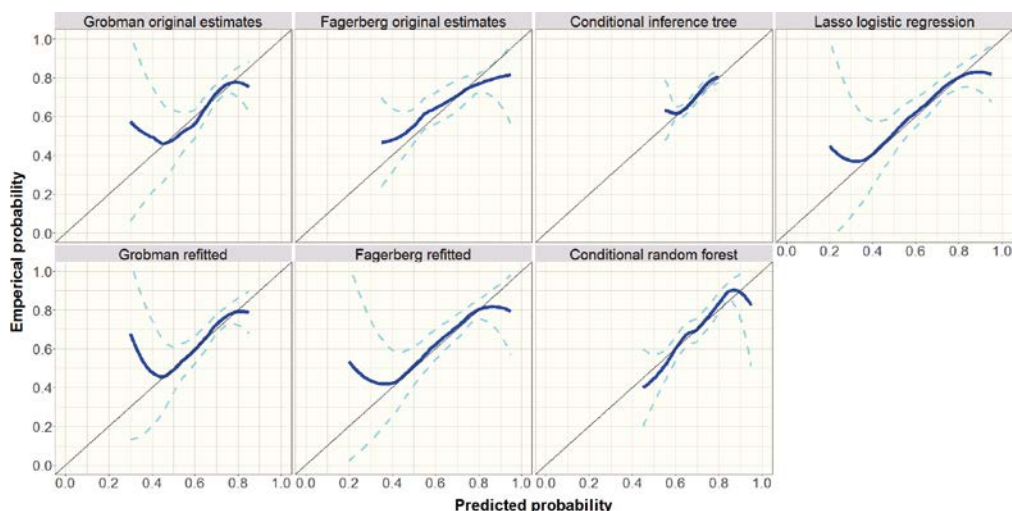
**Table 7.6.** Predictive performance of existing and new predictive models, (95% CI)

Model	AUROC*	Accuracy	Sensitivity	Specificity	5-fold CV accuracy**
<b>Grobman</b> (original estimates)	0.64 (0.61, 0.67)	69.9% (67.6%, 72.2%)	97.6% (96.7%, 98.5%)	7.1% (4.8%, 9.4%)	NA
<b>Grobman</b> (refit model)	0.64 (0.61, 0.67)	69.9% (67.6%, 72.2%)	96.5% (95.4%, 97.6%)	9.6% (7.0%, 12.3%)	69.0% (67.4%, 70.7%)
<b>Fagerberg</b> (original estimates)	0.63 (0.60, 0.66)	70.1% (67.8%, 72.4 %)	91.6% (89.9%, 93.2%)	21.4% (17.7%, 25.1%)	NA
<b>Fagerberg</b> (refit model)	0.66 (0.63, 0.69)	70.7% (68.5%, 73.0%)	93.2% (91.8%, 94.7%)	19.7% (16.1%, 23.3%)	70.1% (68.5%, 71.7%)
Conditional inference tree	0.61 (0.58, 0.63)	69.4% (67.1%, 71.7%)	100.0% (100.0%, 100.0%)	0.0% (0.0%, 0.0%)	68.4% (66.8%, 70.0%)
Random forest	0.69 (0.66, 0.72)	70.0% (67.8%, 72.3%)	97.9% (97.0%, 98.7%)	6.9% (4.6%, 9.2%)	69.9% (68.3%, 71.5%)
Lasso	0.67 (0.64, 0.70)	70.4% (68.1%, 72.7%)	93.4% (92.0%, 94.9%)	18.2% (14.8%, 21.7%)	70.4% (68.8%, 72.0%)

\* AUROC: Area under the receiver-operating characteristics curve

\*\* 5-fold CV accuracy: five-fold cross-validation accuracy

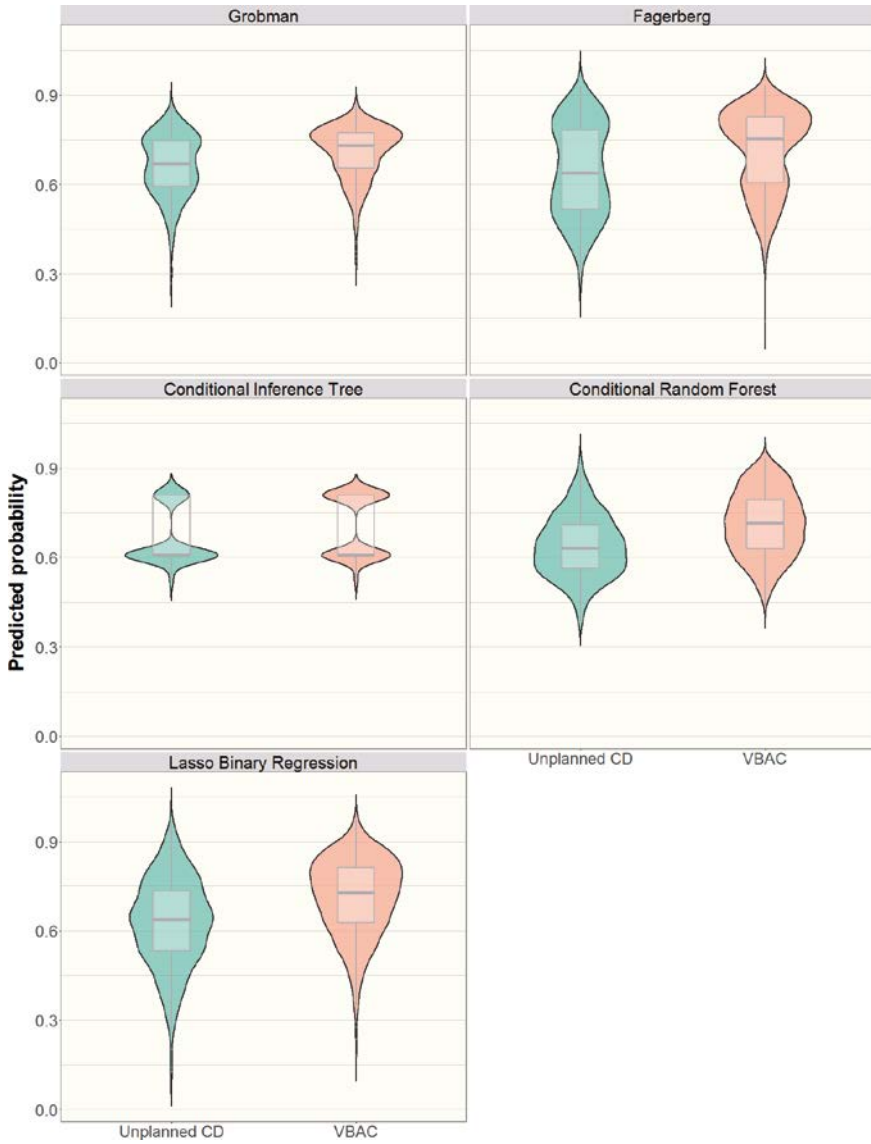
In the calibration plots, all models other than the random forest model deviated from observed CD rates in the lower range of predicted probability (<50%), and all models had wide confidence bands in this lower range (Figure 7.3).



**Figure 7.3.** Calibration plots of the different prediction models. The solid blue line represents the actual performance with dotted 95% confidence bands. Solid grey line is the ideal performance.

In the Grobman and Fagerberg models, 53% and 73% of women with an unplanned repeat CD had a predicted probability of VBAC above 60%. In the conditional inference tree, random forest, and lasso models, 97%, 61%, and 60% of women with unplanned repeat CDs had predicted probabilities of VBAC above 60% (Figure 7.4).

The conditional inference tree first split was at the indication for the first CD and the next split was at the presence of any hypertensive disorder during the second pregnancy. In the random forest, variables with the highest conditional importance included indication for the first CD, onset of labour in the first pregnancy (spontaneous, induction or planned CD), and maternal age, BMI and height. The strongest predictor in the lasso model was a single mother rather than one who was cohabiting in the first pregnancy. However, the model also selected indication of the first CD.



**Figure 7.4.** Violin plot showing the distributions of predicted probability by observed VBAC status for existing and new models. A violin plot is a hybrid of a box plot and a kernel density plot; the box plot in the middle with its median, interquartile range and the rest of the distribution and on the side the kernel density plots showing the distribution shape of the data.



## 8 DISCUSSION

### 8.1 Main Findings

The **time-to-delivery** for nulliparous women induced with transcervical balloon catheter as the first induction method was almost seven hours shorter than for women induced with dinoprostone. Induction with misoprostol was associated with a time-to-delivery that was two hours shorter compared to dinoprostone, which may be of limited clinical importance. However, there was a 24% increased risk of instrumental vaginal delivery. None of the induction methods were associated with maternal or neonatal complications, or with increased **CD rates**, but all the women had overall high rates of CDs independent of the induction method.

Almost 70% of all women undergoing a TOLAC delivered vaginally. Women with an unplanned first CD had 64% increased **risk of repeat CD** in comparison with an elective first CD. Women with a first CD due to labour dystocia ran the greatest risk of a repeat CD. Among these women, a greater cervical dilation at the first CD was associated with an increased chance of a vaginal delivery in the subsequent birth.

Most women with a previous CD scored their **birth experience** as positive irrespective of the 2<sup>nd</sup> mode of delivery. However in comparison with women who had an ERCD, women with an unplanned repeat CD had a five-fold increased risk of a negative birth experience in the 2<sup>nd</sup> birth. Women with two subsequent unplanned CDs were at greatest risk for a negative birth experience.

Our newly developed machine learning models and the refitted previous existing regression models of **predicting VBAC in women with only one previous birth**, a caesarean, had AUROCs of 0.6-0.7. All the models demonstrated a high sensitivity in predicting vaginal delivery but with a low level of specificity, indicating that the prediction of an unplanned repeat CD was poor both for the classical regression models and for the machine learning models. Predictive performance was especially poor below 50% predicted probability, although the misclassification of unplanned repeat CDs spanned the whole range of predicted probability. The majority of women with an unplanned repeat CD had a predicted probability of VBAC above 60%. The original prediction models by Grobman<sup>138</sup> and Fagerberg<sup>139</sup> had a slightly higher AUROC than those in our study, but included women with a previous vaginal birth, which is a strong predictor of VBAC.<sup>117</sup> As we excluded women with the important predictor, a previous vaginal birth, probably made our prediction more difficult.

## 8.2 Methodological considerations

Before applying results to other populations, alternative explanations for the found association with the exposure must be considered. First one should look at the validity of the study and study results. There are two sources of errors in epidemiological studies; systematic and random errors, and these ought to be investigated. After errors have been considered, we can proceed to considering the extent to which our results can be applied to other populations, external validity, or generalisability.

### 8.2.1 Study design

The major strength in **all four studies** in this thesis was the observational, population-based design, where the results derive from the entire population and represent the situation in that population. Our access to prospectively collected data in standardised electronic medical records with information about maternal characteristics, pregnancy and delivery information recorded by midwives or obstetricians before the findings of our studies. This diminishes the risk of selection and recall bias. Thus the population-based design and the use of the electronic medical records strengthens external validity and generalisability through reduced selection bias. With the increasing use of electronic medical records in many countries, our approach is transferable to other contexts where medical records are digitalised. However, there can be a risk of low quality among the registers used in a study, and in general these registers are not based on the study questions nor the study design. Moreover, information in the registers is restricted to what has been entered in the registers. In our case, we are dependent on how rigorous the health care providers enter information into the medical records. However, population-based studies enable us to study rare outcomes and differences that are small as they cover large populations.

### 8.2.2 Systematic and random errors

Errors in epidemiological studies can either be systematic or random. Observational studies have the risk of systematic errors such as selection bias, information bias (misclassification), confounding, effect modification and interaction. These problems have to be avoided and planned for in the beginning of the research process.

#### Selection bias

Selection bias comes from the procedure of selecting or studying subjects, and from factors influencing study participation. When the exposure is assessed prospectively (in advance of the question studied), the risk of selection bias is diminished. In all our studies our exposures (induction method or previous indication for the first CD) were assessed before the outcomes (time-to-delivery, delivery mode, birth experience), thereby making our selection bias low.

### **Information bias/ misclassification**

Inaccurate recording and classification of exposures and outcomes can be information bias or also called, misclassification. If misclassification is the same across the study groups it is random or non-differential, but, if it is unevenly distributed it is referred to as differential. The effect of a non-differential misclassification is that it reduces the differences between the groups and underestimates the true association. In contrast, differential, or non-random misclassifications introduce the possibility of biased estimates in any direction. One common differential misclassification is loss of follow-up, while another type is recall bias, when recall tends to differ according to disease status or outcome. In our studies there are risks of misclassifications, e.g. the indication for the CD reported by the on-call obstetrician, or a surveillance bias due to having a different management of labour if the woman had a history of labour dystocia.

### **Confounding**

Confounding is a central problem in epidemiologic research and occurs when the association between the exposure and outcome is affected by a third factor. Unlike other forms of bias, which are mainly introduced by the investigators or the study participants, confounding is the factor of complex interrelations between exposures and outcomes. The confounding factor is related to both the exposure and the outcome, but may not be found in the causal pathway between exposure and outcome. If this is the case, it is an intermediate factor. Ideally, a confounder can be controlled for by randomization, since the confounders would then be equally distributed between study groups. In observational studies, we can reduce confounding by restrictions, matching, stratification or multivariable analysis.

### **Effect modification or interaction**

Effect modification or interaction refers to when the observed strength of the association between exposure and outcome is affected by a third factor. Effect modification should have a plausible biological explanation and can be difficult to find. It is important that effect modification is discovered, and stratified analyses should be performed to present stratum-specific risk estimates.

### **Random error**

In the absence of systematic errors (bias) observed results can be explained by chance. This is referred as random error. In epidemiological research, to assess the likelihood of random findings, it is usual to calculate a confidence interval for a risk estimate. This confidence interval is usually set to 95%, i.e. there is 95% probability that the association is not explained by chance when the confidence interval for a risk estimate does not include 1.00. Random errors depend on study size.

### 8.2.3 External validity

Internal validity is related to the probability that observed associations are true for the study population itself, while external validity refers to whether results could be generalized to other populations. To generalize the results to other populations, it is of great importance that the internal validity is high through proper handling of bias. External validity is a matter of judgement and discussion, and it depends on the degree of similarity between the study population and the unstudied population.

### 8.2.4 Strengths and limitations in our studies

As described above, a strength of **Study I** is the population-based study design, and in addition, the large sample of more than 7500 induced nulliparous women that enabled us to study our outcomes with high statistical power and diminished the risk of random error. We restricted our analysis to vaginal deliveries and caesarean deliveries due to labour dystocia and induction failure. Excluding caesarean deliveries due to fetal distress (or non-reassurance of fetal well-being) is another strength of our study, since their inclusion would erroneously shorten time-to-delivery.

**Studies II and IV** were conducted in a context of universal maternity care, with only a small variation in the quality of care between hospitals, and a high rate for TOLAC. The relative equal chance for women to perform a TOLAC makes our results more representative, as they are not being affected by the selection that occurs in settings with much lower access to TOLAC. The short study period (2008-2014), constrains the sample size, but the likelihood of great differences in care over time decreases. An important strength in both studies is the large proportion of women performing a TOLAC (almost 60%) of all eligible women, in comparison with international TOLAC rates (US 49%).<sup>106</sup> This gives us adequate statistical power, and further, the fact that we included only women with one previous birth solidified our results, as previous vaginal birth affects VBAC rates.<sup>106</sup>

In **study III** the number of women performing a trial of labour and thereafter succeeding with a VBAC was in line with our study II, conducted in another cohort, and also in line with other previous studies, strengthening the consistency and generalisability of this study.<sup>106</sup>

Today most women are, in Sweden, asked to rate their experience of childbirth before being discharged from the delivery ward. Using the simple, accessible and understandable visual analogue scale (VAS) women score their overall birth experience. VAS is a valid prediction instrument of birth experience and has been shown to be a simple alternative to, and have a high correlation with, other birth experience scales (Wijma Delivery Experience Questionnaire B). It is shown to be consistent over time<sup>126, 164</sup>, and therefore we assumed that the likelihood of measurement bias was low when this method was used for screening. However,

birth experience naturally entails a variety of experiences and feelings in many different dimensions and deeper layers, and it can also change over time.<sup>120,165</sup> For these reasons, it is important to be aware of the limitations of the VAS scale as a tool for deeper understanding of the experience of childbirth. So it may be controversial to investigate the woman's birth experience close to the childbirth and with so simple tools. However, this must be weighed against the high response rates, if scoring occurs before discharge, and the possibility to early find women with low rating of their birth experience.

The purpose of the Swedish Pregnancy Register is to collect data for improvement in both clinical quality and for research.<sup>157</sup> However, as **all studies** are observational with data not collected and designed to the specific study questions, there is always a risk of residual confounding.

**Study I** has limitations typical of observational studies, specifically a risk of misclassification if the delivery was not registered as induction of labour, but the likelihood of this misclassification is uncommon and random. The use of oxytocin was higher in the balloon catheter group and we considered this as a mediator rather than a confounder, and consequently did not adjust for it. The choice of induction method was not done blind in our study and could possibly influence management of labour such as oxytocin augmentation. Further investigations are needed to study the use of oxytocin with different induction methods. Due to limitations in our data, we could not report the number of misoprostol dosages, cumulative oxytocin dose, occurrence of uterine tachysystole and need for tocolysis. We analysed our data on an "intention-to-treat" basis, based on the first induction method, even if induction was continued with a second or third method. This is a limitation but this is also the case with randomised trials. The health provider's methods of choice vary and could influence our results, we adjusted for hospital and calendar year of birth, to minimize this bias. In many countries, misoprostol is not approved as a treatment for the induction of labour, and women seeking information may have found out about this as well as misoprostol's possible adverse effects, thus introducing a selection bias.

The on-call obstetrician performing the first CDs **in our different studies**, reported the indication for the CD, while this does not eliminate the risk of misclassification. As explained previously, to make the correct diagnosis for labour dystocia can be problematic in clinical practice since there are no strict definitions, and as an example to differentiate whether the arrest of labour was due to an induction failure or prolonged first stage can be difficult. But this is unlikely to be systematic and therefore more likely to be a non-differential misclassification. In addition, labour management could have been influenced by previous indications for the first CD as having a history of labour dystocia possibly leads to an earlier decision of repeat CD, introducing surveillance bias, another form of misclassification. Moreover, even before labour, women could have been guaranteed an early decision for

repeat CD if signs of prolonged labour should appear. Furthermore, in **study II**, we have no report on childbirth experience from the first CD, an experience which could affect both TOLAC rates and also the likelihood of vaginal delivery.<sup>152</sup> The preference for an elective repeat CD is multifactorial and contextual<sup>152</sup> and can also depend on socio-economic status and background.<sup>166</sup> These effects of selection bias are partly reduced by adjusting for confounders in the multivariate analysis. In none of the **studies I, II** and **IV** did we have any information on ethnicity, which could be an unmeasured confounder.<sup>167</sup>

In **study II** the effect modification was statistically significant meaning there could be a third factor affecting the association. Here this could indicate that, a woman whose labour needs to be induced already has a sign of abnormality, such as labour dystocia and therefore she has an increased risk of CD, and it is not the induction itself that increases this risk.

In **study III** we included hospitals (12 of 42) with a VAS response rate of 80% or higher. However, these hospitals may not be representative on a nation basis and the small sample size is a limitation. Including all hospitals however would entail the risk of introducing a selection bias on an individual level, e.g. hospitals with low response rate may only ask women when birth experience was putatively negative. We compared women giving birth in included hospitals with and without a VAS score response, and found that women excluded due to no VAS response had similar maternal characteristics and birth outcomes as the women included in our study population. Therefore we concluded that to be scored with VAS in the eligible hospitals was a random selection. The study period in **study II** was short which confines the statistical power of our findings.

## 8.3 In the light of other studies

### Study I

Our main finding in **study I**, that inducing nulliparous women with an unripe cervix using the transcervical balloon catheter is associated with a shorter time from induction to delivery than using prostaglandins, is supported by a randomised controlled trial conducted by Prager et al.<sup>9</sup> Contradictory results were seen in the randomised PROBAAT-II study which showed that that more women induced with misoprostol had delivered within 24 hours compared to women induced with a balloon catheter. However, after 36 hours, a larger proportion of women had delivered within the balloon catheter group.<sup>38</sup> The contradictory results could be explained by the inclusion of women with mixed parity, different misoprostol dosages and intervals of drug administration, and also less fluid filling the balloon catheter<sup>168</sup>, the length of time before the removal of the balloon catheter, and an induction pause during night. In our study we showed that inducing with misoprostol was associated with a greater risk of the need for an instrumental vaginal delivery, in line

with the PROBAAT-II study.<sup>38</sup> In our study, there was a higher rate of maternal infections in the balloon catheter group, but in the adjusted analysis there was no significant difference, aligning with the results from both the PROBAAT-II study and a study by Aghideh et al.<sup>38, 169</sup> Penell et al. showed lower pH in the umbilical cord blood and severe neonatal acidemia within the prostaglandin E2 gel group, compared with the single or double balloon catheter groups. This was interpreted as secondary to the increased rate of uterine hyperstimulation, a finding that was not confirmed in our study.<sup>10</sup>

## Study II

Randomised controlled studies when studying TOLAC and ERCD are ethically dubious, which forces us to depend on results from observational studies. Almost 60% of eligible women chose to attempt a vaginal birth in **study II**, a high rate in comparison with other countries.<sup>52, 95</sup> Previous studies investigating the success rate of TOLAC in women with a history of labour dystocia have contradictory results. According to a study by Hoskins et al. only 13% of women delivered vaginally after a history of CD due to labour dystocia and a fully dilated cervix.<sup>108</sup> Kwon et al. concluded that in women with previous labour dystocia, the degree of cervical dilation did not affect the mode of delivery in a following TOLAC.<sup>110</sup> However, our study and four others convincingly show that cervical dilation in women with labour dystocia at the first CD is associated with the mode of delivery in the following delivery.<sup>109, 111, 112, 116</sup> In line with results from Melamed et al. we also show that women with a first CD due to failed instrumental vaginal delivery had the same risk for repeat CD as all women with a first unplanned CD, and that these women also had a good chance of a VBAC (67.9%, aRR repeat CD 1.62; 95% CI 1.22-2.15).<sup>114</sup> 67% of women performing TOLAC after a first CD due to non-reassuring fetal well-being delivered vaginally, which is in line with 68% in the study by Hoskins et al.<sup>108</sup>

In contrast to our study, most previous studies did not only include women with a first and second delivery. Including women with a previous vaginal delivery makes comparison and interpretation difficult when evaluating a TOLAC attempt.<sup>108, 109, 111, 112, 114</sup> Additionally, most of the studies mentioned were performed in a one centre hospital with local guidelines and practices for dealing with women with a previous CD, which probably affects the results. Our study population is based on seven different hospitals and covers around 25% of all births in Sweden, thus reducing the risk of bias in treatment and increasing the generalisability.

## Study III

Our **study III** confirms and is in line with other studies that show that childbirth experience is associated with the delivery mode in women with a previous CD. Previous studies analysed the effect of an intervention program in women with a previous CD. The intervention consisted of counselling on mode of delivery and

birth outcome.<sup>134-136</sup> These studies had small and clinical-based study populations, were subject to selection bias in opt-in or loss to follow up, or had unadjusted confounding of parity or gestational age.<sup>134-136</sup> Cleary Goldman et al. concluded that women succeeding with a VBAC were most satisfied, but this difference from our results may be explained by the intervention program motivating women to try a TOLAC.<sup>134</sup> Even Shorten et al. concluded that women with a spontaneous vaginal delivery were most satisfied. They asked women 6-8 weeks after delivery thereby giving them the possibility to have time for reflection and perhaps regret the choice of an ERCD. This could be a possible explanation to the difference to our results.<sup>135</sup> However, previous studies do show a consistency of measured birth experience even after time has passed.<sup>164</sup> Shorten et al. had large differences in VBAC success rates (48% versus 74%, expected VBAC rates are internationally 60-80%<sup>53, 97</sup>) at different delivery units, reducing the generalisability of their study.<sup>135</sup> Cleary Goldman et al. only enrolled 95 women of the 316 possible, which makes their study available for selection bias, and including premature births possibly affected birth experience.<sup>134</sup> We included only women with one previous birth and both births at or beyond term. Mixing parity, preterm and term births introduces the risk of diluting the results. Emmet et al. excluded women who did not speak or understand English, which also limits generalisability. They also had a loss to follow up that consisted predominantly of women who were younger and had higher deprivations scores, introducing the risk of selection bias depending on socio-economic factors. However, the results of Emmet et al. were consistent with our results, showing that women with an unplanned repeat CD had the lowest mean VAS score (mean 48.5, scale 0-100).<sup>136</sup> But the mean rating was lower than in our study, possibly due to the context bias when a scale has more states of better or worse, with the risk of depressing or enhancing the values due to cognitive processes used by the respondents.<sup>170</sup> After a counselling program as in the above mentioned studies, awareness and knowledge may increase and birth experience here probably does not reflect the birth experience of a general population, thus diminishing the generalisability of the results. In Sweden, most women are encouraged and recommended to perform a TOLAC after one previous CD, without attending any counselling program during pregnancy.

## Study IV

In **study IV** we excluded women with an earlier vaginal delivery, a strong predictor of VBAC. When comparing our results with the previously existing models by Grobman<sup>138</sup> and Fagerberg<sup>139</sup>, our models would possibly have performed better if we had included women with a previous vaginal delivery. Moreover, despite the additional covariates in our dataset, our models did not perform better than previous classical models, and all today's existing VBAC prediction models perform relatively poorly, indicating that there may also be other factors that affects TOLAC success at a patient, health provider, hospital, and country level, as previous literature provides support for.<sup>150, 171, 172</sup>



## 9 CONCLUSIONS

- Transcervical balloon catheter was associated with a shorter length of labour, from the start of induction to delivery, in comparison to prostaglandins, with no difference in CD rates or adverse maternal or neonatal outcomes. **(Study I)**
- Almost 7 out of 10 women attempting TOLAC delivered vaginally, and even those with a history of labour dystocia had a good chance of vaginal delivery. Reaching a greater cervical dilation in previous birth may not be in vain, as the chance of VBAC is associated with greater cervical dilation. Women attempting a TOLAC might be selected on the basis of an indication for the first CD, but this requires further study. **(Study II)**
- Most women with a previous CD scored their childbirth experience as positive, independent of the second mode of delivery, a result that supports a TOLAC attempt. However, an unplanned repeat CD is associated with a negative childbirth experience. **(Study III)**
- Both classical regression models and machine learning models had a high sensitivity and a low specificity in predicting VBAC in women with only one previous birth, indicating that they are insufficient for predicting unplanned repeat CDs. Additional data covariates combined with machine learning techniques did not improve prediction compared with the classical regression models. VBAC is a difficult prediction problem, as both new and existing models misclassify unplanned repeat CDs across the spectrum of predicted probability. The indication for the first CD still seems to have the strongest association to TOLAC success, strengthening the use of this variable as a decision-maker for TOLAC and that we should emphasize improved birth outcomes in first-time mothers. **(Study IV)**

## 10 FUTURE CHALLENGES

- Since time-to-delivery is an important factor and also an issue with which the clinics must deal with on a daily basis, it would be tempting to study further the effect of using both a transcervical balloon catheter and misoprostol together simultaneously. It would also be interesting to study how women experience this combined induction method with regards to pain and childbirth experience, and to study the duration of delivery, delivery mode and adverse outcomes.
- At my clinic, we take care of the most extreme premature births in Stockholm and sometimes perform a caesarean on women that have only reached 24 gestational weeks. To study these women and their next delivery, to study the TOLAC and VBAC rates, and their birth experience after a previous delivery with an adverse outcome such as an extremely premature birth, would be very interesting and challenging. It would also be valuable to study in more depth their risk of adverse outcomes as uterine rupture, haemorrhage, abruption, abnormal and invasive placentation.
- Further I would like to increase our knowledge about the adverse event uterine rupture. Investigate why in Sweden the incidence is relative high. To study, when during labour the rupture occurs. And the effect of induction and oxytocin use on the risk of uterine rupture.
- Worldwide, hard work is currently underway with an aim to decrease CD rates. Would another form of care for women with a previous CD change the rate of women who dare to attempt a TOLAC? Could an intervention program to inform and educate both the women and the health care providers (midwives and obstetricians) decrease the rate of repeat CDs? Would this change the women's childbirth experiences in a more positive direction? Future studies could aim to study women with a previous CD, how to screen them for their childbirth experience, and if they should be offered counselling before and after birth.
- To predict VBAC would help us in our work motivating and selecting women to undergo a TOLAC. But can we really predict VBAC? Are the existing prediction models of any use? Do obstetricians and midwives more accurately predict an individual women's chances of VBAC than the prediction models that we have today? Future research should focus on prospectively testing different models for predicting VBAC.
- The increasing rate of CDs contributes to the increasing number of women with an invasive placenta. To decide which treatment the woman should undergo is a challenge. It is of great importance to study this, in order to improve birth management for these women.

## 11 POPULÄRVETENSKAPLIG SAMMANFATTNING

Att föda barn är en unik händelse i en kvinnas liv, många ser fram emot förlossningen med blandade känslor av förväntan, glädje och ofta även rädsla. Förlossningen kan påverka kvinnan både fysiskt och psykiskt, och kan även påverka barnets hälsa.<sup>120-124</sup> Sjukvårdens uppgift är att stödja och hjälpa kvinnan under förlossningen. Målsättningen är att undvika onödiga ingripanden, med så låg risk som möjligt för komplikationer i form av sjukdom och död hos kvinnan eller barnet.<sup>71</sup>

Igångsättning av förlossning (induktion) är en vanlig intervention inom förlossningsvården, som har ökat under de senaste decennierna. Idag induceras 19% av alla förlossningar i Sverige.<sup>6, 12, 13</sup> Målet med induktion är att kvinnan ska föda vaginalt innan förlossningen startar spontant. De risker som finns med induktion måste vägas mot de risker som finns för mor och barn att avvakta spontan start.<sup>6</sup> För cirka 10-25% av alla kvinnor som föder sitt första barn med inducerad förlossning, avslutas förlossningen med ett kejsarsnitt.<sup>12</sup> Även kejsarsnitt är en intervention som ökat stadigt de senaste decennierna. Idag avslutas 18% av alla graviditeter i Sverige med ett kejsarsnitt.<sup>2, 5</sup> Orsaken till att inducera en förlossning eller utföra ett kejsarsnitt är ofta densamma eller är sammanlänkade. I förlossningar, efter tidigare förlossning med kejsarsnitt, har kvinnorna och barnet de väntar en ökad risk för komplikationer under såväl graviditeten som under förlossningen.<sup>52, 95, 97</sup>

I de flesta länder anses det säkert för kvinnor, med ett tidigare kejsarsnitt, att föda vaginalt vid efterföljande förlossning.<sup>53, 97, 104</sup> När kvinnan försöker föda vaginalt, avslutas förlossningen med antingen en vaginal förlossning eller ett upprepat kejsarsnitt. Risken för komplikationer vid försök att föda vaginalt är dock förhöjd. Till exempel kan det gamla kejsarsnittsärret på livmodern brista (uterusruptur) med risk för allvarliga komplikationer hos både kvinnan och barnet. Frekvensen uterusruptur varierar något. I en stor amerikansk studie från 2004 fick 0.7% av 17 898 kvinnor, som försökte föda vaginalt, efter ett tidigare kejsarsnitt, en uterusruptur. I samma studie, ådrog sig 12 barn hjärnskador på grund av syrebrist under förlossningen. Hos 7 av barnen berodde syrebristen på uterusruptur. I en svensk undersökning fick 1.3% av kvinnorna med ett tidigare kejsarsnitt en uterusruptur.<sup>96</sup> Komplikationer utöver uterusruptur uppstår till större del hos kvinnorna som genomgår ett upprepat kejsarsnitt, t.ex. infektion i livmodern eller stora blödningar med behov av blodtransfusioner.<sup>95</sup> Många kvinnor vill inte föda vaginalt efter ett tidigare kejsarsnitt och väljer därför ett planerat kejsarsnitt. Men även ett planerat kejsarsnitt innebär en ökad risk för komplikationer såsom infektioner, större blödning, borttagning av livmodern, blodpropp och till och med död hos kvinnan.<sup>91</sup>

Det övergripande syftet med denna avhandling är att öka kunskapen om hur det går för kvinnor, som föder sitt andra barn efter ett tidigare kejsarsnitt. Mina medförfattare i de olika studierna och jag har studerat sambandet mellan orsaken till kejsarsnitt i den första förlossningen och förlossningssättet i den andra förlossningen, samt risken för ett upprepat kejsarsnitt och en negativ förlossningsupplevelse. Därtill har vi, med hjälp av artificiell intelligens, utvecklat modeller för att beräkna varje kvinnas individuella chans att föda vaginalt efter ett tidigare kejsarsnitt.

Eftersom 10-25% av alla förstföderskor i Sverige som induceras föder med kejsarsnitt<sup>12</sup>, jämförde vi tre olika induktionsmetoders tid från induktion till förlossning och respektive metods risk för kejsarsnitt.

### **Studie I: Tid till förlossning efter induktion och risk för kejsarsnitt, jämförelse utav tre metoder**

I studie I undersöktes 7551 förstföderskor, som blev inducerade i Stockholm eller Gotland mellan 2008 och 2014. Kvinnornas barn var fullgångna, låg i huvudbjudning och föddes levande. Eftersom kvinnornas livmoderhals var omogen för förlossning, inducerades de med en av följande tre metoder; 1) vaginalt applicerad dinoprostone (vår referensmetod enligt för tiden gällande riktlinjer) 2) oral tablett misoprostol 3) ballongkateter. Både dinoprostone och misoprostol är prostaglandiner, ett läkemedel som mjukar upp livmoderhalsen. Ballongkatetern som appliceras genom livmoderhalsen och fylls med vätska ovanför inre modernmunnen, genererar ett mekaniskt tryck på livmoderhalsen samt stimulerar kvinnans egna hormoner att utsöndras för att få livmoderhalsen att mogna inför förlossningen.

Resultaten visade att tiden från induktion till förlossning var knappt sju timmar kortare med ballongkateter i jämförelse med dinoprostone. Vid jämförelse mellan dinoprostone och misoprostol var tiden två timmar kortare med misoprostol. Detta efter att vi korrigerat resultaten för andra faktorer som kan påverka tiden till förlossning.

Av kvinnorna som erhöll ballong födde 95% inom 24 timmar. Av de som erhöll misoprostol födde endast 55% inom 24 timmar, och för de som fick dinoprostone endast 54 % inom 24 timmar. Vi fann ingen skillnad i antalet kejsarsnitt mellan de tre metoderna, men misoprostol var associerat med 24% högre risk för förlossning med sugklocka jämfört med dinoprostone.

### **Studie2: Risk för upprepat kejsarsnitt**

I studie 2 födde 5302 kvinnor mellan 2008 och 2014 både sitt första och andra barn i Stockholm eller på Gotland. Det första barnet föddes antingen med planerat eller akut kejsarsnitt. Inför den andra förlossningen var barnen fullgångna, låg i huvudbjudning och föddes levande. Av dessa 5302 kvinnor var det drygt 41%

som direkt valde ett planerat kejsarsnitt inför andra förlossningen. Resterande 59% (3116 kvinnor) försökte föda vaginalt. Dessa kvinnor utgjorde vår studiepopulation.

Vi fann att av alla kvinnor i studiepopulationen födde till slut 69% vaginalt. De kvinnor som hade ett första planerat kejsarsnitt födde till största del vaginalt i andra förlossningen. I jämförelse med kvinnorna som hade ett första planerat kejsarsnitt löpte de kvinnor som kejsarsnittades akut på grund av värksvaghet nästan dubbelt så stor risk för upprepat kejsarsnitt vid andra förlossningen. Hos kvinnor med värksvaghet vid första kejsarsnittet fann vi ett samband mellan hur mycket livmoderhalsen öppnade sig före förlossningen avbröts, och risken för upprepat kejsarsnitt. Risken för upprepat kejsarsnitt var högst hos kvinnor med ett första akut kejsarsnitt och induktion av andra förlossningen.

### **Studie III: Risk för negativ förlossningsupplevelse**

I studie III använde vi oss av Graviditetsregistret, ett nytt register sedan 2013 och med idag 98,5% av Sveriges alla förlossningar registrerade.<sup>12, 156</sup> Vi studerade kvinnor med ett tidigare kejsarsnitt och deras förlossningsupplevelse i andra förlossningen. Vid många av förlossningsklinikerna i Sverige ber man den nyförlösta kvinnan skatta sin förlossningsupplevelse innan hon lämnar kliniken. På klinikerna används en enkel, lättförståelig, visuell analog skala (VAS) där kvinnan ger ett poäng mellan 1 och 10, där 1 är värsta tänkbara och 10 är bästa tänkbara förlossningsupplevelse. Vid våra första analyser fann vi att vissa regioner hade låg svarsfrekvens av förlossningsupplevelsen och andra regioner hade omvänd tolkning av VAS-skalan. Vi sorterade därför bort klinikerna med omvänd tolkning av VAS-skalan och även alla kliniker med en svarsfrekvens som var lägre än 80% sorterades bort. Av de 42 kliniker som fanns registrerade i Graviditetsregistret hade vi slutligen endast 12 kliniker kvar, med sammanlagt 780 kvinnor, som fött både sitt första och andra barn vid någon av dessa kliniker under 2014-2017. Dessa kvinnor utgjorde vår studiepopulation. De inkluderade klinikerna var jämt spridda över Sverige och utgjorde en blandning av såväl universitetskliniker som mindre förlossningskliniker.

Även i denna studie såg vi att sju av tio kvinnor som försökte föda vaginalt efter ett första kejsarsnitt födde vaginalt vid andra förlossningen. Oavsett förlossnings-sätt vid andra förlossningen skattade de flesta kvinnor sin förlossningsupplevelse högt, med VAS poäng 8 eller högre. Sedan tidigare är det visat att ca 10% av alla kvinnor upplever sin förlossning som negativ.<sup>120, 159</sup> I vår studie hade 10% av alla kvinnor skattat förlossningen till 5 poäng eller lägre, således satte vi gränsen för negativ förlossningsupplevelse vid 5 poäng eller lägre.

I jämförelse med kvinnor som födde andra barnet med planerat kejsarsnitt, fann vi att kvinnor som födde sitt andra barn med akut kejsarsnitt var risken för negativ förlossningsupplevelse upp till 5 gånger högre.

## **Studie IV: Prediktion av vaginal förlossning hos tidigare kejsarsnittade kvinnor**

I studie IV studerade vi samma population som i studie II och som bestod av 3116 tidigare kejsarsnittade kvinnor som försökte föda sitt andra barn vaginalt. Med hjälp av artificiell intelligens utvecklade vi tre olika modeller för att försöka förut-säga (predicera) den enskilda kvinnans möjligheter att föda vaginalt efter endast ett tidigare kejsarsnitt. Våra nya modeller jämförde vi med en äldre modell utvecklad i USA (Grobmans modell<sup>138</sup>), som använder vanlig statistisk regressionsanalys för prediktion. Vi jämförde även våra nya modeller med Fagerbergs modell<sup>139</sup>, en vidare-utveckling av Grobmans modell, utvecklad för att användas i ett svenskt sammanhang. Både Grobmans och Fagerbergs modell anpassade vi till studiepopulationen i vår databas. Därefter jämförde vi de äldre modellerna med de nya avseende förmågan att predicera vaginal förlossning hos kvinnor med endast ett tidigare kejsarsnitt.

Våra resultat visade att alla modeller hade en hög sensitivitet d.v.s. hög förmåga att predicera vaginal förlossning. Samtliga modeller hade dock en låg specificitet d.v.s. låg förmåga att förutsäga ett upprepat kejsarsnitt. Av den anledningen analyserade vi vidare. Vi fann, med Grobmans modell, att 53% av alla kvinnor som födde med upprepat kejsarsnitt hade egentligen blivit predicerade till mer än 60% chans att föda vaginalt. I Fagerbergs modell var 73% av kvinnorna med upprepat kejsarsnitt predicerade till mer än 60% chans att föda vaginalt. Våra nya modeller hade ungefär lika stor del felprediktion som Grobmans och Fagerbergs modeller. Våra nya modeller, utvecklade med hjälp av artificiell intelligens och avancerade statistiska metoder, med tillgång till en stor mängd information om kvinnornas graviditeter, tidigare förlossning och det första barnet förbättrade tyvärr inte prediktionen.

## **Slutsatser**

- Induktion med ballongkateter var hos förstföderskor associerat med kortast tid till förlossning jämfört med prostaglandiner. Vi fann ingen skillnad mellan induktion med prostaglandiner eller ballongkateter i varken kejsarsnittsfrekvens eller andra allvarliga komplikationer hos mor eller barn.
- Nästan sju av tio kvinnor som försökte föda vaginalt efter ett tidigare kejsarsnitt födde vaginalt. Även om det första kejsarsnittet utfördes p.g.a. värksvaghet hade dessa kvinnor en god chans att föda vaginalt vid efterföljande förlossning. Störst chans av de värksvaga kvinnorna hade de vars livmoderhals öppnat sig mest innan det första kejsarsnittet utfördes. Kvinnor med tidigare kejsarsnitt kan möjligen selekteras för ett vaginalt förlossningsförsök beroende på orsaken till första kejsarsnittet.

- De flesta kvinnor med ett tidigare kejsarsnitt var nöjda med sin nästföljande förlossning oavsett förlossningssätt. Men ett akut upprepat kejsarsnitt efter att ha försökt föda vaginalt var associerat med ökad risk för negativ förlossningsupplevelse. Kvinnor med tidigare kejsarsnitt kan vara en utsatt grupp och bör tillfrågas om sin förlossningsupplevelse och följas upp vid behov.
- Både klassiska prediktionsmodeller baserade på regressionanalys och våra nya modeller utvecklade med hjälp av artificiell intelligens, hade hög sensitivitet att predicera vaginal förlossning hos kvinnor med endast ett tidigare kejsarsnitt. Men samtliga modeller var dåliga på att förutse upprepat kejsarsnitt. Trots mängden data våra nyutvecklade modeller använde för att predicera vaginal förlossning presterade de inte bättre än de äldre traditionella modellerna. Både de gamla och nya modellerna felklassificerar upprepat kejsarsnitt över hela prediktionsspektrat. Det verkar som om orsaken till första kejsarsnittet har den starkaste associationen till förlossningssätt vid nästa graviditet. Vi bör därför lägga mycket resurser på förstföderskans förlossning och förbättra hennes förlossningsutfall.

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## 13 REFERENCES

1. Miller S, Abalos E, Chamillard M, Ciapponi A, Colaci D, Comande D, et al. Beyond too little, too late and too much, too soon: a pathway towards evidence-based, respectful maternity care worldwide. *Lancet* (London, England). 2016 Oct 29;388(10056):2176-92.
2. WHO Department of Reproductive Health and Research. WHO Statement on Caesarean Section Rates. 2015.
3. Tracy SK, Sullivan E, Wang YA, Black D, Tracy M. Birth outcomes associated with interventions in labour amongst low risk women: a population-based study. *Women and birth : journal of the Australian College of Midwives*. 2007 Jun;20(2):41-8.
4. Rossignol M, Chaillet N, Boughrassa F, Moutquin JM. Interrelations between four antepartum obstetric interventions and cesarean delivery in women at low risk: a systematic review and modeling of the cascade of interventions. *Birth* (Berkeley, Calif). 2014 Mar;41(1):70-8.
5. Swedish National Board of Health and Welfare. Kejsarsnitt i Sverige 1990–2001. Socialstyrelsen. Research report. 2005.
6. Swedish National Board of Health and Welfare. Official Statistics of Sweden. Pregnancies, Deliveries and Newborn Infants. The Swedish Medical Birth Register 1973-2015. Graviditeter, förlossningar och nyfödda barn. Medicinska födelseregistret 1973–2015. Socialstyrelsen. 2017.
7. Yeast JD, Jones A, Poskin M. Induction of labor and the relationship to cesarean delivery: A review of 7001 consecutive inductions. *American journal of obstetrics and gynecology*. 1999 Mar;180(3 Pt 1):628-33.
8. Glantz JC. Term labor induction compared with expectant management. *Obstetrics and gynecology*. 2010 Jan;115(1):70-6.
9. Prager M, Eneroth-Grimfors E, Edlund M, Marions L. A randomised controlled trial of intravaginal dinoprostone, intravaginal misoprostol and transcervical balloon catheter for labour induction. *BJOG : an international journal of obstetrics and gynaecology*. 2008 Oct;115(11):1443-50.
10. Pennell CE, Henderson JJ, O'Neill MJ, McChlery S, Doherty DA, Dickinson JE. Induction of labour in nulliparous women with an unfavourable cervix: a randomised controlled trial comparing double and single balloon catheters and PGE2 gel. *BJOG : an international journal of obstetrics and gynaecology*. 2009 Oct;116(11):1443-52.

11. Thorsell M, Lyrenas S, Andolf E, Kaijser M. Induction of labor and the risk for emergency cesarean section in nulliparous and multiparous women. *Acta obstetricia et gynecologica Scandinavica*. 2011 Oct;90(10):1094-9.
12. The Swedish Pregnancy Register. Årsrapport. Graviditetsregistret 2018. 2019.
13. Practice Bulletin No. 107: Induction of labor. ACOG. *Obstetrics and gynecology*. 2009 Aug;114(2 Pt 1):386-97.
14. National Institute for Health and Clinical Excellence: Guidance. Induction of Labour. London: RCOG Press. National Collaborating Centre for Women's and Children's Health.; 2008.
15. Vahratian A, Zhang J, Troendle JF, Sciscione AC, Hoffman MK. Labor progression and risk of cesarean delivery in electively induced nulliparas. *Obstetrics and gynecology*. 2005 Apr;105(4):698-704.
16. Dare MR, Middleton P, Crowther CA, Flenady VJ, Varatharaju B. Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). The Cochrane database of systematic reviews. 2006 Jan 25(1):Cd005302.
17. Hannah ME, Ohlsson A, Farine D, Hewson SA, Hodnett ED, Myhr TL, et al. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. TERMPROM Study Group. *The New England journal of medicine*. 1996 Apr 18;334(16):1005-10.
18. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bokedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet (London, England)*. 2009 Sep 19;374(9694):979-88.
19. Stock SJ, Ferguson E, Duffy A, Ford I, Chalmers J, Norman JE. Outcomes of elective induction of labour compared with expectant management: population based study. *BMJ (Clinical research ed)*. 2012 May 10;344:e2838.
20. Mishanina E, Rogozinska E, Thatthi T, Uddin-Khan R, Khan KS, Meads C. Use of labour induction and risk of cesarean delivery: a systematic review and meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2014 Jun 10;186(9):665-73.
21. Grobman WA, Rice MM, Reddy UM, Tita ATN, Silver RM, Mallett G, et al. Labor Induction versus Expectant Management in Low-Risk Nulliparous Women. *The New England journal of medicine*. 2018 Aug 9;379(6):513-23.

22. Middleton P, Shepherd E, Crowther CA. Induction of labour for improving birth outcomes for women at or beyond term. The Cochrane database of systematic reviews. 2018 May 9;5:Cd004945.
23. Keulen JK, Bruinsma A, Kortekaas JC, van Dillen J, Bossuyt PM, Oudijk MA, et al. Induction of labour at 41 weeks versus expectant management until 42 weeks (INDEX): multicentre, randomised non-inferiority trial. *BMJ (Clinical research ed)*. 2019 Feb 20;364:1344.
24. Elden H, Hagberg H, Wessberg A, Sengpiel V, Herbst A, Bullarbo M, et al. Study protocol of SWEPIs a Swedish multicentre register based randomised controlled trial to compare induction of labour at 41 completed gestational weeks versus expectant management and induction at 42 completed gestational weeks. *BMC pregnancy and childbirth*. 2016 Mar 7;16:49.
25. Boulvain M, Irion O, Dowswell T, Thornton JG. Induction of labour at or near term for suspected fetal macrosomia. The Cochrane database of systematic reviews. 2016 May 22(5):Cd000938.
26. Boulvain M, Senat MV, Perrotin F, Winer N, Beucher G, Subtil D, et al. Induction of labour versus expectant management for large-for-date fetuses: a randomised controlled trial. *Lancet (London, England)*. 2015 Jun 27;385(9987):2600-5.
27. Magro-Malosso ER, Saccone G, Chen M, Navathe R, Di Tommaso M, Berghella V. Induction of labour for suspected macrosomia at term in non-diabetic women: a systematic review and meta-analysis of randomised controlled trials. *BJOG : an international journal of obstetrics and gynaecology*. 2017 Feb;124(3):414-21.
28. Norwitz ER. Induction of labour for fetal macrosomia: do we finally have an answer? *BJOG : an international journal of obstetrics and gynaecology*. 2017 Feb;124(3):422.
29. Moldeus K, Cheng YW, Wikstrom AK, Stephansson O. Induction of labor versus expectant management of large-for-gestational-age infants in nulliparous women. *PloS one*. 2017;12(7):e0180748.
30. Cheng YW, Delaney SS, Hopkins LM, Caughey AB. The association between the length of first stage of labor, mode of delivery, and perinatal outcomes in women undergoing induction of labor. *American journal of obstetrics and gynecology*. 2009 Nov;201(5):477.e1-7.
31. Danforth DN, Veis A, Breen M, Weinstein HG, Buckingham JC, Manalo P. The effect of pregnancy and labor on the human cervix: changes in collagen, glycoproteins, and glycosaminoglycans. *American journal of obstetrics and gynecology*. 1974 Nov 1;120(5):641-51.

32. Bishop EH. PELVIC SCORING FOR ELECTIVE INDUCTION. *Obstetrics and gynecology*. 1964 Aug;24:266-8.
33. Crane JM. Factors predicting labor induction success: a critical analysis. *Clinical obstetrics and gynecology*. 2006 Sep;49(3):573-84.
34. Alfirevic Z, Aflaifel N, Weeks A. Oral misoprostol for induction of labour. *The Cochrane database of systematic reviews*. 2014;6:Cd001338.
35. Manabe Y. Laminaria tent for gradual and safe cervical dilatation. *American journal of obstetrics and gynecology*. 1971 Jul 1;110(5):743-5.
36. Jozwiak M, Bloemenkamp KW, Kelly AJ, Mol BW, Irion O, Bouvain M. Mechanical methods for induction of labour. *The Cochrane database of systematic reviews*. 2012;3:Cd001233.
37. Jozwiak M, Oude Rengerink K, Benthem M, van Beek E, Dijksterhuis MG, de Graaf IM, et al. Foley catheter versus vaginal prostaglandin E2 gel for induction of labour at term (PROBAAT trial): an open-label, randomised controlled trial. *Lancet (London, England)*. 2011 Dec 17;378(9809):2095-103.
38. Ten Eikelder ML, Oude Rengerink K, Jozwiak M, de Leeuw JW, de Graaf IM, van Pampus MG, et al. Induction of labour at term with oral misoprostol versus a Foley catheter (PROBAAT-II): a multicentre randomised controlled non-inferiority trial. *Lancet (London, England)*. 2016 Apr 16;387(10028):1619-28.
39. Hill MG, Gonzalez MG, Lo-Ciganic WH, Reed KL. Misoprostol in Addition to a Double-Balloon Catheter for Induction: A Double-Blind Randomized Controlled Trial. *American journal of perinatology*. 2017 Sep 14.
40. Moldin PG, Sundell G. Induction of labour: a randomised clinical trial of amniotomy versus amniotomy with oxytocin infusion. *British journal of obstetrics and gynaecology*. 1996 Apr;103(4):306-12.
41. Howarth GR, Botha DJ. Amniotomy plus intravenous oxytocin for induction of labour. *The Cochrane database of systematic reviews*. 2001(3):Cd003250.
42. Caldeyro-Barcia R. Oxytocin in pregnancy and labour. *Acta endocrinologica Supplementum*. 1960;34(Suppl 50):41-9.
43. Bouvain M, Stan C, Irion O. Membrane sweeping for induction of labour. *The Cochrane database of systematic reviews*. 2001(2):Cd000451.
44. Kavanagh J, Kelly AJ, Thomas J. Sexual intercourse for cervical ripening and induction of labour. *The Cochrane database of systematic reviews*. 2001(2):Cd003093.



45. Smith CA, Armour M, Dahlen HG. Acupuncture or acupressure for induction of labour. The Cochrane database of systematic reviews. 2017 Oct 17;10:Cd002962.
46. Hapangama D, Neilson JP. Mifepristone for induction of labour. The Cochrane database of systematic reviews. 2009 Jul 08(3):Cd002865.
47. Lurie S. The changing motives of cesarean section: from the ancient world to the twenty-first century. Archives of gynecology and obstetrics. 2005 Apr;271(4):281-5.
48. Sewell JE. Cesarean Section - a brief history. NIH US National Library of Medicine for ACOG. 1998.
49. Swedish society for Obstetrics and Gynecology (SFOG). Cesarean Section. Kejsarsnitt. ARG-rapport Nr 65. 2010.
50. Högberg U. Maternal deaths related to cesarean section in Sweden, 1951-1980. AOGS. 1989;1989;68:351-357.
51. Cragin E. Conservatism in obstetrics. NY Med J. 1916;1916;104:1-3.
52. Practice bulletin no. 115: Vaginal birth after previous cesarean delivery. ACOG. Obstetrics and gynecology. 2010 Aug;116(2 Pt 1):450-63.
53. Practice Bulletin No. 184: Vaginal Birth After Cesarean Delivery. ACOG. Obstetrics and gynecology. 2017 Nov;130(5):e217-e33.
54. Landon MB, Grobman WA. What We Have Learned About Trial of Labor After Cesarean Delivery from the Maternal-Fetal Medicine Units Cesarean Registry. Seminars in perinatology. 2016 Aug;40(5):281-6.
55. Robson MS. Can we reduce the caesarean section rate? Best practice & research Clinical obstetrics & gynaecology. 2001 Feb;15(1):179-94.
56. Betran AP, Vindevoghel N, Souza JP, Gulmezoglu AM, Torloni MR. A systematic review of the Robson classification for caesarean section: what works, doesn't work and how to improve it. PloS one. 2014;9(6):e97769.
57. Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the increasing cesarean delivery rate. Obstetrics and gynecology. 2011 Jul;118(1):29-38.
58. Gifford DS, Morton SC, Fiske M, Keesey J, Keeler E, Kahn KL. Lack of progress in labor as a reason for cesarean. Obstetrics and gynecology. 2000 Apr;95(4):589-95.

59. Laughon SK, Branch DW, Beaver J, Zhang J. Changes in labor patterns over 50 years. *American journal of obstetrics and gynecology*. 2012 May;206(5):419.e1-9.
60. Sandstrom A, Cnattingius S, Wikstrom AK, Stephansson O. Labour dystocia--risk of recurrence and instrumental delivery in following labour--a population-based cohort study. *BJOG : an international journal of obstetrics and gynaecology*. 2012 Dec;119(13):1648-56.
61. Sandström A. Labour dystocia: Risk factors and consequences for mother and infant. Thesis for doctoral degree Karolinska Institutet. 2016.
62. ACOG. Dystocia and augmentation of labor. ACOG. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2004 Jun;85(3):315-24.
63. Practice Bulletin Number 49, December 2003: Dystocia and augmentation of labor. ACOG. *Obstetrics and gynecology*. 2003 Dec;102(6):1445-54.
64. Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary cesarean delivery. *American journal of obstetrics and gynecology*. 2014 Mar;210(3):179-93.
65. National Institute for Health and Care Excellence: Clinical Guidelines. Intrapartum Care: Care of Healthy Women and Their Babies During Childbirth. London: National Institute for Health and Care Excellence (UK) Copyright (c) 2014 National Collaborating Centre for Women's and Children's Health.; 2014.
66. Swedish National Board of Health and Welfare. Normal labour practice. In Swedish: Handläggning av normal förlossning. State of the Art. Socialstyrelsen. 2001.
67. Le Ray C, Audibert F, Goffinet F, Fraser W. When to stop pushing: effects of duration of second-stage expulsion efforts on maternal and neonatal outcomes in nulliparous women with epidural analgesia. *American journal of obstetrics and gynecology*. 2009 Oct;201(4):361.e1-7.
68. Cheng YW, Hopkins LM, Caughey AB. How long is too long: Does a prolonged second stage of labor in nulliparous women affect maternal and neonatal outcomes? *American journal of obstetrics and gynecology*. 2004 Sep;191(3):933-8.
69. Allen VM, Baskett TF, O'Connell CM, McKeen D, Allen AC. Maternal and perinatal outcomes with increasing duration of the second stage of labor. *Obstetrics and gynecology*. 2009 Jun;113(6):1248-58.

70. Rouse DJ, Weiner SJ, Bloom SL, Varner MW, Spong CY, Ramin SM, et al. Second-stage labor duration in nulliparous women: relationship to maternal and perinatal outcomes. *American journal of obstetrics and gynecology*. 2009 Oct;201(4):357.e1-7.
71. WHO Guidelines Approved by the Guidelines Review Committee. WHO recommendations: Intrapartum care for a positive childbirth experience. Geneva: World Health Organization Copyright (c) World Health Organization 2018.; 2018.
72. Alfirevic Z, Devane D, Gyte GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. *The Cochrane database of systematic reviews*. 2013 May 31(5):Cd006066.
73. Vintzileos AM, Nochimson DJ, Guzman ER, Knuppel RA, Lake M, Schiffrin BS. Intrapartum electronic fetal heart rate monitoring versus intermittent auscultation: a meta-analysis. *Obstetrics and gynecology*. 1995 Jan;85(1):149-55.
74. Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. *Lancet (London, England)*. 2000 Oct 21;356(9239):1375-83.
75. Berhan Y, Haileamlak A. The risks of planned vaginal breech delivery versus planned caesarean section for term breech birth: a meta-analysis including observational studies. *BJOG : an international journal of obstetrics and gynaecology*. 2016 Jan;123(1):49-57.
76. Od lind V, Haglund B, Pakkanen M, Otterblad Olausson P. Deliveries, mothers and newborn infants in Sweden, 1973-2000. Trends in obstetrics as reported to the Swedish Medical Birth Register. *Acta obstetrica et gynecologica Scandinavica*. 2003 Jun;82(6):516-28.
77. Sjogren B. Reasons for anxiety about childbirth in 100 pregnant women. *Journal of psychosomatic obstetrics and gynaecology*. 1997 Dec;18(4):266-72.
78. Rouhe H, Salmela-Aro K, Gissler M, Halmesmaki E, Saisto T. Mental health problems common in women with fear of childbirth. *BJOG : an international journal of obstetrics and gynaecology*. 2011 Aug;118(9):1104-11.
79. Lukasse M, Vangen S, Oian P, Kumle M, Ryding EL, Schei B. Childhood abuse and fear of childbirth--a population-based study. *Birth (Berkeley, Calif)*. 2010 Dec;37(4):267-74.
80. Stjernholm YV, Petersson K, Eneroth E. Changed indications for cesarean sections. *Acta obstetrica et gynecologica Scandinavica*. 2010;89(1):49-53.

81. Silver RM. Abnormal Placentation: Placenta Previa, Vasa Previa, and Placenta Accreta. *Obstetrics and gynecology*. 2015 Sep;126(3):654-68.
82. Thurn L, Lindqvist PG, Jakobsson M, Colmorn LB, Klungsoyr K, Bjarnadottir RI, et al. Abnormally invasive placenta-prevalence, risk factors and antenatal suspicion: results from a large population-based pregnancy cohort study in the Nordic countries. *BJOG : an international journal of obstetrics and gynaecology*. 2016 Jul;123(8):1348-55.
83. National Institute for Health and Clinical Excellence: Guidance. Caesarean Section. London: RCOG Press. National Collaborating Centre for Women's and Children's Health.; 2011.
84. Tita AT. When is primary cesarean appropriate: maternal and obstetrical indications. *Seminars in perinatology*. 2012 Oct;36(5):324-7.
85. Barrett JF. Twin delivery: method, timing and conduct. *Best practice & research Clinical obstetrics & gynaecology*. 2014 Feb;28(2):327-38.
86. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. *Obstetrics and gynecology*. 2011 Mar;117(3):618-26.
87. Fellman V, Hellstrom-Westas L, Norman M, Westgren M, Kallen K, Lagercrantz H, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. *Jama*. 2009 Jun 03;301(21):2225-33.
88. Hakansson S, Farooqi A, Holmgren PA, Serenius F, Hogberg U. Proactive management promotes outcome in extremely preterm infants: a population-based comparison of two perinatal management strategies. *Pediatrics*. 2004 Jul;114(1):58-64.
89. Simpson LL. When is primary cesarean appropriate: fetal indications. *Seminars in perinatology*. 2012 Oct;36(5):328-35.
90. Liu S, Liston RM, Joseph KS, Heaman M, Sauve R, Kramer MS. Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2007 Feb 13;176(4):455-60.
91. Gregory KD, Jackson S, Korst L, Fridman M. Cesarean versus vaginal delivery: whose risks? Whose benefits? *American journal of perinatology*. 2012 Jan;29(1):7-18.

92. Confidential Enquiry into Maternal and Child Health. Why Mother Die 2000–2002: The Sixth Report of the Confidential Enquiry into Maternal Death in the United Kingdom. London. RCOG Press. 2004.
93. Hall MH, Bewley S. Maternal mortality and mode of delivery. *Lancet* (London, England). 1999 Aug 28;354(9180):776.
94. WHO Guidelines Approved by the Guidelines Review Committee. WHO Recommendations for the Prevention and Treatment of Postpartum Haemorrhage. Geneva: World Health Organization.; 2012.
95. Landon MB, Hauth JC, Leveno KJ, Spong CY, Leindecker S, Varner MW, et al. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. *The New England journal of medicine*. 2004 Dec 16;351(25):2581-9.
96. Hesselman S, Hogberg U, Ekholm-Selling K, Rassjo EB, Jonsson M. The risk of uterine rupture is not increased with single- compared with double-layer closure: a Swedish cohort study. *BJOG : an international journal of obstetrics and gynaecology*. 2015 Oct;122(11):1535-41.
97. Green-top Guideline No. 45. Birth After Previous Caesarean Birth. RCOG. 2015 October 2015.
98. Committee opinion no. 529: placenta accreta. *Obstetrics and gynecology*. 2012 Jul;120(1):207-11.
99. Silver RM, Landon MB, Rouse DJ, Leveno KJ, Spong CY, Thom EA, et al. Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstetrics and gynecology*. 2006 Jun;107(6):1226-32.
100. RCOG. Placenta praevia, placenta praevia accreta and vasa praevia: diagnosis and management. Guideline No 27, 2011. 2011.
101. Silver RM. Delivery after previous cesarean: long-term maternal outcomes. *Seminars in perinatology*. 2010 Aug;34(4):258-66.
102. Hesselman S, Hogberg U, Rassjo EB, Schytt E, Lofgren M, Jonsson M. Abdominal adhesions in gynaecologic surgery after caesarean section: a longitudinal population-based register study. *BJOG : an international journal of obstetrics and gynaecology*. 2018 Apr;125(5):597-603.
103. Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. *British journal of obstetrics and gynaecology*. 1995 Feb;102(2):101-6.

104. Cunningham FG, Bangdiwala SI, Brown SS, Dean TM, Frederiksen M, Rowland Hogue CJ, et al. NIH consensus development conference draft statement on vaginal birth after cesarean: new insights. NIH consensus and state-of-the-science statements. 2010 Mar 10;27(3):1-42.
105. Lydon-Rochelle MT, Cahill AG, Spong CY. Birth after previous cesarean delivery: short-term maternal outcomes. *Seminars in perinatology*. 2010 Aug;34(4):249-57.
106. Landon MB, Leindecker S, Spong CY, Hauth JC, Bloom S, Varner MW, et al. The MFMU Cesarean Registry: factors affecting the success of trial of labor after previous cesarean delivery. *American journal of obstetrics and gynecology*. 2005 Sep;193(3 Pt 2):1016-23.
107. Grobman WA. Rates and prediction of successful vaginal birth after cesarean. *Seminars in perinatology*. 2010 Aug;34(4):244-8.
108. Hoskins IA, Gomez JL. Correlation between maximum cervical dilatation at cesarean delivery and subsequent vaginal birth after cesarean delivery. *Obstetrics and gynecology*. 1997 Apr;89(4):591-3.
109. Bujold E, Gauthier RJ. Should we allow a trial of labor after a previous cesarean for dystocia in the second stage of labor? *Obstetrics and gynecology*. 2001 Oct;98(4):652-5.
110. Kwon JY, Jo YS, Lee GS, Kim SJ, Shin JC, Lee Y. Cervical dilatation at the time of cesarean section may affect the success of a subsequent vaginal delivery. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2009 Nov;22(11):1057-62.
111. Abildgaard H, Ingerslev MD, Nickelsen C, Secher NJ. Cervical dilation at the time of cesarean section for dystocia -- effect on subsequent trial of labor. *Acta obstetrica et gynecologica Scandinavica*. 2013 Feb;92(2):193-7.
112. Lewkowitz AK, Nakagawa S, Thiet MP, Rosenstein MG. Effect of stage of initial labor dystocia on vaginal birth after cesarean success. *American journal of obstetrics and gynecology*. 2015 Dec;213(6):861.e1-5.
113. Duff P, Southmayd K, Read JA. Outcome of trial of labor in patients with a single previous low transverse cesarean section for dystocia. *Obstetrics and gynecology*. 1988 Mar;71(3 Pt 1):380-4.
114. Melamed N, Segev M, Hadar E, Peled Y, Wiznitzer A, Yogev Y. Outcome of trial of labor after cesarean section in women with past failed operative vaginal delivery. *American journal of obstetrics and gynecology*. 2013 Jul;209(1):49.e1-7.

115. Ollendorff DA, Goldberg JM, Minogue JP, Socol ML. Vaginal birth after cesarean section for arrest of labor: is success determined by maximum cervical dilatation during the prior labor? *American journal of obstetrics and gynecology*. 1988 Sep;159(3):636-9.
116. Impey L, O'Herlihy C. First delivery after cesarean delivery for strictly defined cephalopelvic disproportion. *Obstetrics and gynecology*. 1998 Nov;92(5):799-803.
117. Caughey AB, Shipp TD, Repke JT, Zelop C, Cohen A, Lieberman E. Trial of labor after cesarean delivery: the effect of previous vaginal delivery. *American journal of obstetrics and gynecology*. 1998 Oct;179(4):938-41.
118. West HM, Jozwiak M, Dodd JM. Methods of term labour induction for women with a previous caesarean section. *The Cochrane database of systematic reviews*. 2017 Jun 09;6:Cd009792.
119. Dodd JM, Crowther CA, Grivell RM, Deussen AR. Elective repeat caesarean section versus induction of labour for women with a previous caesarean birth. *The Cochrane database of systematic reviews*. 2017 Jul 26;7:Cd004906.
120. Waldenstrom U, Borg IM, Olsson B, Skold M, Wall S. The childbirth experience: a study of 295 new mothers. *Birth (Berkeley, Calif)*. 1996 Sep;23(3):144-53.
121. Downe S, Finlayson K, Oladapo OT, Bonet M, Gulmezoglu AM. What matters to women during childbirth: A systematic qualitative review. *PloS one*. 2018;13(4):e0194906.
122. Bossano CM, Townsend KM, Walton AC, Blomquist JL, Handa VL. The maternal childbirth experience more than a decade after delivery. *American journal of obstetrics and gynecology*. 2017 Sep;217(3):342.e1-.e8.
123. Gottvall K, Waldenstrom U. Does a traumatic birth experience have an impact on future reproduction? *BJOG : an international journal of obstetrics and gynaecology*. 2002 Mar;109(3):254-60.
124. de Graaff LF, Honig A, van Pampus MG, Stramrood CAI. Preventing post-traumatic stress disorder following childbirth and traumatic birth experiences: a systematic review. *Acta obstetrica et gynecologica Scandinavica*. 2018 Jun;97(6):648-56.
125. Elvander C, Cnattingius S, Kjerulff KH. Birth experience in women with low, intermediate or high levels of fear: findings from the first baby study. *Birth (Berkeley, Calif)*. 2013 Dec;40(4):289-96.

126. Larsson C, Saltvedt S, Edman G, Wiklund I, Andolf E. Factors independently related to a negative birth experience in first-time mothers. *Sexual & reproductive healthcare : official journal of the Swedish Association of Midwives*. 2011 Apr;2(2):83-9.
127. Aasheim V, Waldenstrom U, Rasmussen S, Schytt E. Experience of childbirth in first-time mothers of advanced age - a Norwegian population-based study. *BMC pregnancy and childbirth*. 2013 Feb 27;13:53.
128. Henriksen L, Grimsrud E, Schei B, Lukasse M. Factors related to a negative birth experience - A mixed methods study. *Midwifery*. 2017 Aug;51:33-9.
129. Nystedt A, Hildingsson I. Women's and men's negative experience of child birth-A cross-sectional survey. *Women and birth : journal of the Australian College of Midwives*. 2018 Apr;31(2):103-9.
130. Hildingsson I, Karlstrom A, Nystedt A. Women's experiences of induction of labour--findings from a Swedish regional study. *The Australian & New Zealand journal of obstetrics & gynaecology*. 2011 Apr;51(2):151-7.
131. Waldenstrom U, Hildingsson I, Rubertsson C, Radestad I. A negative birth experience: prevalence and risk factors in a national sample. *Birth (Berkeley, Calif)*. 2004 Mar;31(1):17-27.
132. Kjerulff KH, Brubaker LH. New mothers' feelings of disappointment and failure after cesarean delivery. *Birth (Berkeley, Calif)*. 2018 Mar;45(1):19-27.
133. Karlstrom A. Women's self-reported experience of unplanned caesarean section: Results of a Swedish study. *Midwifery*. 2017 Jul;50:253-8.
134. Cleary-Goldman J, Cornelisse K, Simpson LL, Robinson JN. Previous cesarean delivery: understanding and satisfaction with mode of delivery in a subsequent pregnancy in patients participating in a formal vaginal birth after cesarean counseling program. *American journal of perinatology*. 2005 May;22(4):217-21.
135. Shorten A, Shorten B. The importance of mode of birth after previous cesarean: success, satisfaction, and postnatal health. *Journal of midwifery & women's health*. 2012 Mar-Apr;57(2):126-32.
136. Emmett CL, Montgomery AA, Murphy DJ. Preferences for mode of delivery after previous caesarean section: what do women want, what do they get and how do they value outcomes? *Health expectations : an international journal of public participation in health care and health policy*. 2011 Dec;14(4):397-404.
137. Grobman WA, Lai Y, Landon MB, Spong CY, Leveno KJ, Rouse DJ, et al. Prediction of uterine rupture associated with attempted vaginal birth after cesarean delivery. *American journal of obstetrics and gynecology*. 2008 Jul;199(1):30.e1-5.



138. Grobman WA, Lai Y, Landon MB, Spong CY, Leveno KJ, Rouse DJ, et al. Development of a nomogram for prediction of vaginal birth after cesarean delivery. *Obstetrics and gynecology*. 2007 Apr;109(4):806-12.
139. Fagerberg MC, Marsal K, Kallen K. Predicting the chance of vaginal delivery after one cesarean section: validation and elaboration of a published prediction model. *European journal of obstetrics, gynecology, and reproductive biology*. 2015 May;188:88-94.
140. Deo RC. Machine Learning in Medicine. *Circulation*. 2015 Nov 17;132(20):1920-30.
141. Obermeyer Z, Emanuel EJ. Predicting the Future - Big Data, Machine Learning, and Clinical Medicine. *The New England journal of medicine*. 2016 Sep 29;375(13):1216-9.
142. Darcy AM, Louie AK, Roberts LW. Machine Learning and the Profession of Medicine. *Jama*. 2016 Feb 9;315(6):551-2.
143. Lemon SC, Roy J, Clark MA, Friedmann PD, Rakowski W. Classification and regression tree analysis in public health: methodological review and comparison with logistic regression. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine*. 2003 Dec;26(3):172-81.
144. James G, Witten D, Hastie T, Tibshirani R. *An introduction to statistical learning*: Springer; 2013.
145. Petersen ML, van der Laan MJ. Causal models and learning from data: integrating causal modeling and statistical estimation. *Epidemiology (Cambridge, Mass)*. 2014;25(3):418.
146. Rose S. A machine learning framework for plan payment risk adjustment. *Health services research*. 2016;51(6):2358-74.
147. Kominiarek MA, VanVeldhuisen P, Gregory K, Fridman M, Kim H, Hibbard JU. Intrapartum cesarean delivery in nulliparas: risk factors compared by two analytical approaches. *Journal of perinatology : official journal of the California Perinatal Association*. 2015 Mar;35(3):167-72.
148. Breiman L. Random Forests. *Machine Learning*. 2001 October 01;45(1):5-32.
149. Hu C, Steingrimsson JA. Personalized Risk Prediction in Clinical Oncology Research: Applications and Practical Issues Using Survival Trees and Random Forests. *Journal of biopharmaceutical statistics*. 2017 Oct 19:1-17.
150. Yee LM, Liu LY, Grobman WA. Relationship between obstetricians' cognitive and affective traits and delivery outcomes among women with a prior cesarean. *American journal of obstetrics and gynecology*. 2015 Sep;213(3):413.e1-7.

151. Yee LM, Kaimal AJ, Houston KA, Wu E, Thiet MP, Nakagawa S, et al. Mode of delivery preferences in a diverse population of pregnant women. *American journal of obstetrics and gynecology*. 2015 Mar;212(3):377.e1-24.
152. Shorten A, Shorten B, Kennedy HP. Complexities of choice after prior cesarean: a narrative analysis. *Birth (Berkeley, Calif)*. 2014 Jun;41(2):178-84.
153. Gilbert SA, Grobman WA, Landon MB, Varner MW, Wapner RJ, Sorokin Y, et al. Lifetime cost-effectiveness of trial of labor after cesarean in the United States. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2013 Sep-Oct;16(6):953-64.
154. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European journal of epidemiology*. 2009;24(11):659-67.
155. Stephansson O, Sandstrom A, Petersson G, Wikstrom AK, Cnattingius S. Prolonged second stage of labour, maternal infectious disease, urinary retention and other complications in the early postpartum period. *BJOG : an international journal of obstetrics and gynaecology*. 2016 Mar;123(4):608-16.
156. The Swedish Pregnancy Register. Verksamhetsberättelse Graviditetsregistret 2017. Graviditetsregistretse. 2017.
157. Stephansson O, Petersson K, Bjork C, Conner P, Wikstrom AK. The Swedish Pregnancy Register - for quality of care improvement and research. *Acta obstetrica et gynecologica Scandinavica*. 2018 Apr;97(4):466-76.
158. Grobman WA, Lai Y, Landon MB, Spong CY, Leveno KJ, Rouse DJ, et al. Does information available at admission for delivery improve prediction of vaginal birth after cesarean? *American journal of perinatology*. 2009 Nov;26(10):693-701.
159. Waldenstrom U, Nilsson CA. Experience of childbirth in birth center care. A randomised controlled study. *Acta obstetrica et gynecologica Scandinavica*. 1994 Aug;73(7):547-54.
160. Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: A conditional inference framework. *Journal of Computational and Graphical statistics*. 2006;15(3):651-74.
161. Strobl C, Boulesteix A-L, Kneib T, Augustin T, Zeileis A. Conditional variable importance for random forests. *BMC bioinformatics*. 2008;9(1):307.
162. Tibshirani R. Regression shrinkage and selection via the lasso. *Journal of the Royal Statistical Society: Series B (Methodological)*. 1996;58(1):267-88.

163. WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. 2013 Originally 1964.
164. Turkmen S, Tjernstrom M, Dahmoun M, Bolin M. Post-partum duration of satisfaction with childbirth. *The journal of obstetrics and gynaecology research*. 2018 Jul 29.
165. Waldenstrom U. Women's memory of childbirth at two months and one year after the birth. *Birth (Berkeley, Calif)*. 2003 Dec;30(4):248-54.
166. Chen MM, Hancock H. Women's knowledge of options for birth after Caesarean Section. *Women and birth : journal of the Australian College of Midwives*. 2012 Sep;25(3):e19-26.
167. Juarez SP, Small R, Hjern A, Schytt E. Caesarean Birth is Associated with Both Maternal and Paternal Origin in Immigrants in Sweden: a Population-Based Study. *Paediatric and perinatal epidemiology*. 2017 Nov;31(6):509-21.
168. Delaney S, Shaffer BL, Cheng YW, Vargas J, Sparks TN, Paul K, et al. Labor induction with a Foley balloon inflated to 30 mL compared with 60 mL: a randomised controlled trial. *Obstetrics and gynecology*. 2010 Jun;115(6):1239-45.
169. Aghideh FK, Mullin PM, Ingles S, Ouzounian JG, Oppen N, Wilson ML, et al. A comparison of obstetrical outcomes with labor induction agents used at term. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2014 Apr;27(6):592-6.
170. Torrance GW, Feeny D, Furlong W. Visual analog scales: do they have a role in the measurement of preferences for health states? *Medical decision making : an international journal of the Society for Medical Decision Making*. 2001 Jul-Aug;21(4):329-34.
171. Wu E, Kaimal AJ, Houston K, Yee LM, Nakagawa S, Kuppermann M. Strength of preference for vaginal birth as a predictor of delivery mode among women who attempt a vaginal delivery. *American journal of obstetrics and gynecology*. 2014 May;210(5):440.e1-6.
172. Thornton P. Limitations of Vaginal Birth After Cesarean Success Prediction. *Journal of midwifery & women's health*. 2018 Jan;63(1):115-20.